



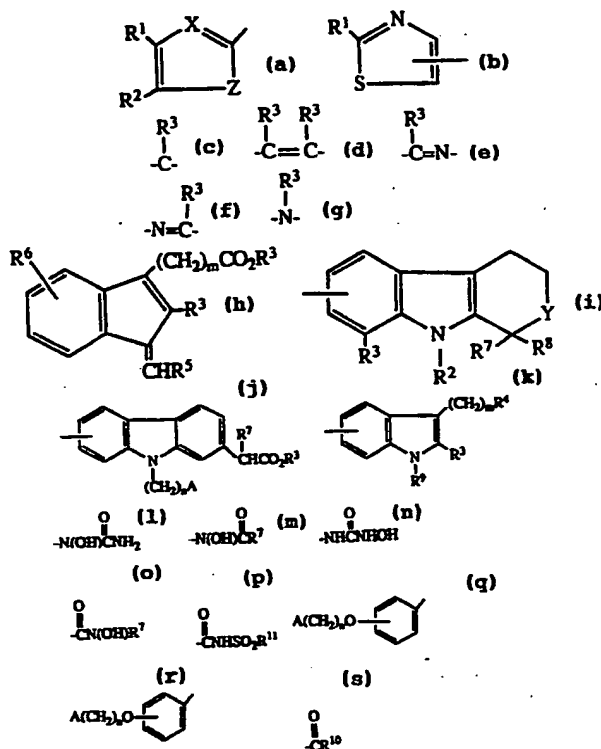
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 215/14, 209/22 A61K 31/47, C07D 403/12 C07D 401/14, 409/12, 491/04 // (C07D 491/04, 311/00, 209/00)		A2	(11) International Publication Number: WO 91/06537
(21) International Application Number: PCT/US90/06251		(43) International Publication Date: 16 May 1991 (16.05.91)	
(22) International Filing Date: 27 October 1990 (27.10.90)		(74) Agents: ALICE, Ronald, W. et al.; American Home Products Corporation, 685 Third Avenue, New York, NY 10017 (US).	
(30) Priority data: 428,260 27 October 1989 (27.10.89) US 596,134 11 October 1990 (11.10.90) US		(81) Designated States: AT (European patent), AU, BE (European patent), BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), SU.	
(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; 685 Third Avenue, New York, NY 10017 (US).		Published Without international search report and to be republished upon receipt of that report.	
(72) Inventors: MUSSER, John, Henry ; 544 Winchester Drive, Yardley, PA 19067 (US). KREFT, Anthony, Frank, III ; 43 Barley Court, Langhorne, PA 19046 (US). FAILLI, Amedeo, Arturo ; 14 Landing Lane, Princeton Junction, NJ 08550 (US). DEMERSON, Christopher, Alexander ; 19 Gervais Street, Kirkland, Quebec H9H 4Z9 (US). SHAH, Uresh, Shantilal ; 166 Thoreau Drive, Plainsboro, NJ 08536 (US). NELSON, James, Albert ; 7 Decision Way West, Washington Crossing, PA 18977 (US).			

(54) Title: SUBSTITUTED INDOLE-, INDENE-, PYRANOINDOLE- AND TETRAHYDROCARBAZOLE- ALKANOIC ACID DERIVATIVES AS INHIBITORS OF PLA₂ AND LIPOXYGENASE

(57) Abstract

There are disclosed compounds of the formula: A(CH₂)_nO-B, wherein A is C₄-C₈ alkyl, phenoxyethyl, phenoxyphenyl or a group having formula (a) or (b), wherein X is -N- or (c); Z is (d), (e), (f), (g), -S- or -O-; R¹ is hydrogen, lower alkyl, phenyl or phenyl substituted with trifluoromethyl; R² is hydrogen or lower alkyl; or R¹ and R² taken together form a benzen ring; R³ is hydrogen or lower alkyl; n is 1-2; B is (h), (i), (j) or (k); wherein R⁴ is -CO₂R², (l), (m), (n), (o) or (p); m is 0-3; R⁵ is (q); or phenyl or phenyl substituted by halo, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl; R⁶ is A(CH₂)_nO- or halo; with the proviso that when R⁶ is halo, R⁵ is (r); R⁷ is lower alkyl; Y is -CH₂- or -O-; R⁸ is lower alkyl or -(CH₂)_mCO₂R³; R⁹ is (s) or -CH₂R¹⁰; R¹⁰ is lower alkyl, phenyl, phenyl substituted with carboxy, halo, loweralkylthio or loweralkylsulfinyl, pyridyl, furanyl or quinolinyl; R¹¹ is lower alkyl or phenyl; and the pharmacologically acceptable salts thereof, and their use in the treatment of inflammatory conditions, such as rheumatoid arthritis, ulcerative colitis, psoriasis and other immediate hypersensitivity reactions; in the treatment of leukotriene-mediated naso-bronchial obstructive air-pasageway conditions, such as allergic rhinitis, allergic bronchial asthma and the like; and as gastric cytoprotective agents.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MR	Mauritania
BE	Belgium	GA	Gabon	MW	Malawi
BF	Burkina Faso	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	SD	Sudan
CF	Central African Republic	KP	Democratic People's Republic of Korea	SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LJ	Liechtenstein	SU	Soviet Union
CI	Côte d'Ivoire	LK	Sri Lanka	TD	Chad
CM	Cameroon	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

**SUBSTITUTED INDOLE-, INDENE-, PYRANOINDOLE- AND
TETRAHYDROCARBAZOLE- ALKANOIC ACID DERIVATIVES
AS INHIBITORS OF PLA₂ AND LIPOXYGENASE**

5

This invention relates to novel substituted indene-, indole-, pyrano-indole- and tetrahydrocarbazole alkanolic acid derivatives possessing lipoxygenase inhibitory, phospholipase A₂ inhibitory and leukotriene antagonist activity, which are useful as anti-inflammatory, antiallergic and cytoprotective agents.

10

It is now well-established that arachidonic acid (AA) is metabolized in mammals by two distinct pathways. The metabolism of arachidonic acid by cyclooxygenase enzymes results in the production of prostaglandins and thromboxanes. The physiological activity of the prostaglandins has already been amply elucidated in recent years. It is now known that prostaglandins arise from the endoperoxides PGG₂ and PGH₂ by the cyclooxygenase pathway of arachidonic acid metabolism. These endoperoxides are also the precursors of the thromboxanes (Tx) A₂ and B₂. TxA₂ is a vasoconstrictor which stimulates platelet aggregation. In the normal situation, the vasoconstrictive and platelet aggregating properties of the thromboxanes are balanced by another product arising from the endoperoxides in the cyclooxygenase pathway, prostacyclin (PGI₂), which is a vasodilator with platelet aggregation inhibitory activity. In the event prostacyclin synthesis is impaired and/or platelet activation is enhanced, then thrombosis and vasoconstriction is favored. The role of prostanoids in haemostasis and thrombosis are reviewed by R.J. Gryglewski, *CRC Crit. Rev. Biochem.*, **7**, 291 (1980) and J. B. Smith, *Am. J. Pathol.*, **99**, 743 (1980). Cyclooxygenase metabolites are known to participate directly in the inflammatory response [see Higgs et al., *Annals of Clinical Research*, **16**, 287-299 (1984)]. This is through their vasodepressor activities, participation in pain and fever augmentation of peptide mediator vascular permeability and edema forming properties. Finally, various aspects of cell mediated immunity are influenced by cyclooxygenase products.

20

25

30

35

The other pathway of AA metabolism involves lipoxygenase enzymes and results in the production of a number of oxidative products called leukotrienes. The latter are designated by the LT nomenclature system, and the most significant products of the lipoxygenase metabolic pathway are the leukotrienes B₄, C₄ and D₄. The substance denominated slow-reacting substance of anaphylaxis (SRS-A) has been shown to consist of a mixture of leukotrienes, with LTC₄ and LTD₄ as the primary products and having varying amounts of other leukotriene metabolites [see Bach et al.,

J. Immun., 215, 115-118 (1980); Biochem. Biophys. Res. Commun., 93, 1121-1126 (1980)].

The significance of these leukotrienes is that a great deal of evidence has been accumulated showing that leukotrienes participate in inflammatory reactions, exhibit chemotactic activities, stimulate lysosomal enzyme release and act as important factors in the immediate hypersensitivity reaction. It has been shown that LTC₄ and LTD₄ are potent bronchoconstrictors of the human bronchi [see Dahlen et al., Nature, 288, 484-486 (1980) and Piper, Int. Arch. Appl. Immunol., 76, suppl. 1, 43 (1985)] which stimulate the release of mucus from airways *in vitro* [Marom et al., Am. Rev. Resp. Dis., 126, 449 (1982)], are potent vasodilators in skin [see Bisgaard et al., Prostaglandins, 23, 797 (1982)], and produce a wheal and flare response [Camp et al., Br. J. Pharmacol., 80, 497 (1983)]. The nonpeptide leukotriene, LTB₄, is a powerful chemotactic factor for leukocytes [see A. W. Ford-Hutchinson, J. Roy. Soc. Med., 74, 831-833 (1981), which stimulates cell accumulation and affects vascular smooth muscle [see Bray, Br. Med. Bull., 39, 249 (1983)]. The activity of leukotrienes as mediators of inflammation and hypersensitivity is extensively reviewed in Bailey and Casey, Ann. Reports Med. Chem., 19, 87 (1986).

Phospholipase A₂ (PLA₂) is the critical rate limiting enzyme in the arachidonic acid (AA) cascade since it is responsible for the hydrolysis of esterified AA from the C-2 position of membrane phospholipids. This reaction generates two products (1) free AA which is then available for subsequent metabolism by either the cyclooxygenase or lipoxygenase enzymes and (2) lysophospholipid. When alkyl-arachidonoyl-glycerophosphatidylcholine is acted upon by the PLA₂ the generation of platelet activating factor (PAF) is initiated; PAF is pro-inflammatory in its own right [see Wedmore et al., Br. J. Pharmacol., 74, 916-917 (1981)]. In this regard it may be noted that the anti-inflammatory steroids are thought to inhibit eicosanoid synthesis by inducing the synthesis of a PLA₂ inhibitory protein denominated macrocortin or lipomodulin [see Flower et al., Nature, London, 278, 456 (1979) and Hirata et al., Proc. Natn. Acad. Sci. U.S.A., 77, 2533 (1980)].

As the initial step leading to subsequent conversion of AA to the various eicosanoids by the cyclooxygenase and lipoxygenase pathways, the PLA₂-mediated release of AA from membrane phospholipids is a critical event in attempting to deal with the various physiological manifestations which are based on the activity of the eicosanoids and/or PAF. Thus, while PLA₂ has been shown to be required for platelet aggregation [Pickett et al., Biochem. J., 160, 405 (1976)], cardiac contraction and excitation [Geisler et al., Pharm. Res. Commun., 9, 117 (1977)], as well as

- 3 -

prostaglandin synthesis [Vogt, Adv. Prostagl. Thromb. Res., 3, 89 (1978)], the inhibition of PLA₂ is indicated in the therapeutic treatment of both PAF induced or cyclooxygenase and/or lipoxygenase pathway product-mediated physiological conditions.

5 There is also evidence that products of the cyclooxygenase/lipoxygenase pathways play key roles in both the pathogenesis of gastric mucosal damage due to extracellular (gastric and intestinal contents, microorganisms, and the like) or intra-cellular (ischemia, viruses, etc.) agents, as well as in cytoprotection against such damage. Thus, on the one hand prostaglandins exert a cytoprotective effect on the
10 gastric mucosa [see Robert, Gastroenterology, 77, 761-767 (1979)] and this action of the prostaglandins, especially of the E series, is considered to be of importance in the treatment of gastro-intestinal ulceration [see Isselbacher, Drugs, 33 (suppl.), 38-46 (1987)]. On the other hand, *ex vivo* experiments have shown that gastric mucosal tissue from ethanol-pretreated rats is capable of LTC₄ generation and that this LTC₄
15 production is quantitatively related to the severity of the ethanol damage [see Lange et al., Naunyn-Schmiedeberg's Arch. Pharmacol. Suppl., 330, R27, (1985)]. It has also been demonstrated that LTC₄ can induce vasoconstriction in both venous and arteriolar vessels in the rat submucosa [see Whittle, IUPHAR Ninth Int. Cong. of Pharm., S30-2, London, England (1984)]. This is significant since ethanol-induced lesion formation
20 in gastric mucosa may be multifactorial with, for example, stasis of gastric blood flow contributing significantly to the development of the hemorrhagic necrotic aspects of the tissue injury [see Guth et al., Gastroenterology, 87, 1083-90 (1984)]. Moreover, in the anesthetized cat, exogenous LTD₄ evokes both increased pepsin secretion and decreased transgastric potential [Pendleton et al., Eur. J. Pharmacol., 125, 297-99
25 (1986)]. A particularly significant recent finding in this regard is that 5-lipoxygenase inhibitors and some leukotriene antagonists protect the gastric mucosa against lesions induced by the oral or parenteral administration of most nonsteroidal anti-inflammatory drugs [see Rainsford, Agents and Actions, 21, 316-319 (1987)]. Platelet activating factor (PAF) is also implicated as a mediator of gastrointestinal damage, and it has been
30 recently shown that 5-lipoxygenase inhibitors inhibit PAF-induced gastric mucosal damage (Gastroenterology, 96, A55, A434, 1989). Accordingly, a significant body of evidence implicates the involvement of lipoxygenase products in the development of pathological features associated with gastric mucosal lesions, such as for example, those induced by ethanol exposure and administration of non-steroidal anti-inflamma-
35 tory drugs. Thus, compounds which inhibit the biological effects of leukotrienes and

- 4 -

PAF and/or which control the biosynthesis of these substances, as by inhibiting 5-lipoxygenase, are considered to be of value as cytoprotective agents.

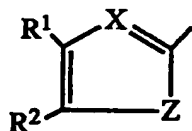
Accordingly, the biological activity of the leukotrienes and SRS's, and of lipoxygenase as the enzyme leading to the metabolism of AA to leukotrienes, indicates that a rational approach to drug therapy to prevent, remove or ameliorate the symptoms of allergies, anaphylaxis, asthma and inflammation and for gastric cytoprotection must focus on either blocking the release of mediators of these conditions or antagonizing their effects. Thus, compounds which inhibit the biological effects of the leukotrienes and SRS's and/or which control the biosynthesis of these substances, as by inhibiting the PLA₂-mediated release of arachidonic acid from membrane phospholipids, or by inhibiting lipoxygenase, are considered to be of value in treating such conditions as allergic bronchial asthma, allergic rhinitis, as well as in other immediate hypersensitivity reactions and in providing gastric cytoprotection.

It has now been found that certain novel substituted indene-, indole-, pyranoindole- and tetrahydrocarbazole alkanolic acid derivatives inhibit PLA₂ and lipoxygenase, and antagonize products of the lipoxygenase pathway, and so are useful as anti-inflammatory, anti-allergic and cytoprotective agents. The present invention provides novel compounds having the following formula:

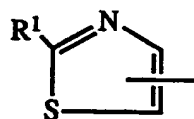


wherein

A is C₄-C₈ alkyl, phenoxyethyl, phenoxyphenyl or a group having the formula



or



wherein

X is -N- or -C-^{R³};

Z is -C^{R³}=C^{R³}-, -C^{R³}=N^{R³}-, -N^{R³}=C^{R³}-, -N^{R³}-, -S- or -O-;

R¹ is hydrogen, lower alkyl, phenyl or phenyl substituted with trifluoromethyl;

R² is hydrogen or lower alkyl; or

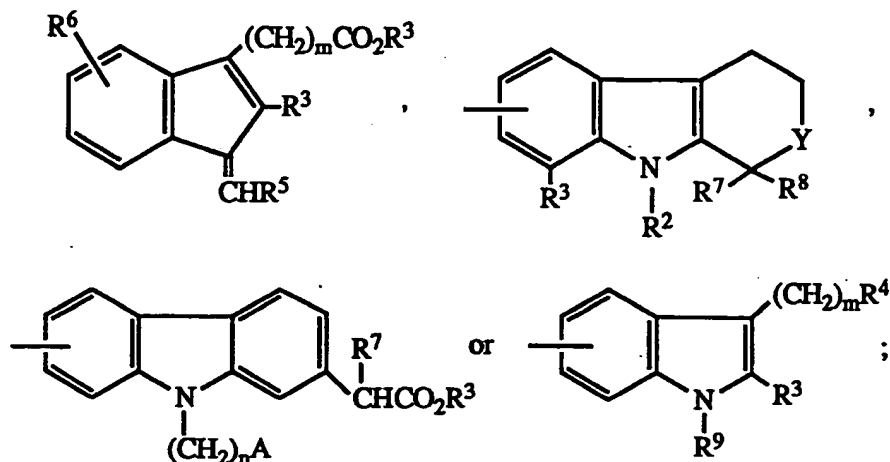
R¹ and R² taken together form a benzene ring;

R³ is hydrogen or lower alkyl;

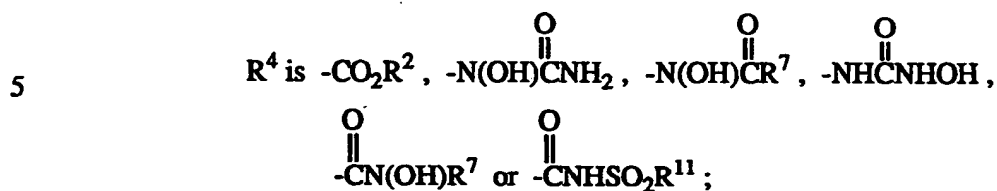
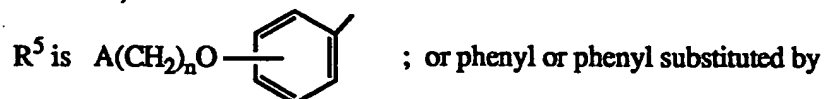
n is 1 - 2;

- 5 -

B is

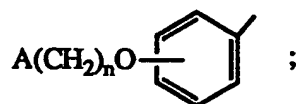
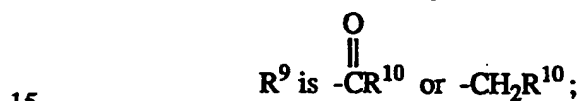


wherein

 m is 0 - 3;

halo, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl;

10 R^6 is $\text{A}(\text{CH}_2)_n\text{O}-$ or halo; with the proviso that when R^6 is halo, R^5 is

 R^7 is lower alkyl; Y is $-\text{CH}_2-$ or $-\text{O}-$; R^8 is lower alkyl or $-(\text{CH}_2)_m\text{CO}_2R^3$;

R^{10} is lower alkyl, phenyl, phenyl substituted with carboxy, halo, loweralkylthio or loweralkylsulfinyl, pyridyl, furanyl or quinolinyl;

 R^{11} is lower alkyl or phenyl;

20 and the pharmacologically acceptable salts thereof.

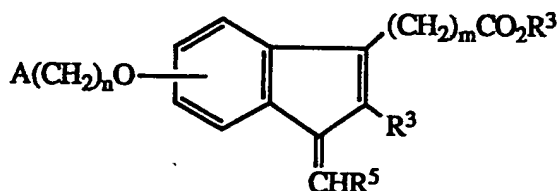
- 6 -

The terms "lower alkyl" and "lower alkoxy" refer to moieties having 1-6 carbon atoms in the carbon chain. The term "halo" refers to fluoro, chloro or bromo.

The grouping A embraces, inter alia, 5- or 6- membered unsaturated nitrogen, sulfur or oxygen containing mono- or benzofused-heterocycles, optionally substituted with lower alkyl or phenyl. The foregoing definition embraces the following heterocyclic moieties: furyl, pyrrolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, benzofuranyl, benzothienyl, benzothiazolyl, indolyl, benzoxazolyl, quinoliny, quinazolinyl, benzimidazolyl, quinoxaliny, quinazolinyl and the like. Especially preferred are quinoliny, benzothiazolyl, benzimidazolyl and 2-phenylthiazole.

The compounds of the invention can form pharmacologically acceptable salts from pharmacologically acceptable organic and inorganic acids such as hydrochloric, hydrobromic, sulfonic, sulfuric, phosphoric, nitric, maleic, fumaric, benzoic, ascorbic, pamoic, succinic, methanesulfonic, acetic, propionic, tartaric, citric, lactic, malic, mandelic, cinnamic, palmitic, itaconic and benzenesulfonic. The compounds which are carboxylic acids are capable of forming alkali metal and alkaline earth carboxylates and carboxylates of pharmacologically acceptable cations derived from ammonia or a basic amine. Examples of the latter include but are not limited to cations such as ammonium, mono-, di-, and trimethylammonium, mono-, di- and triethylammonium, mono-, di- and tripropylammonium (iso and normal), ethyldimethylammonium, benzyldimethylammonium, cyclohexylammonium, benzylammonium, dibenzylammonium, piperidinium, morpholinium, pyrrolidinium, piperazinium, 1-methylpiperidinium, 4-ethylmorpholinium, 1-isopropylpyrrolidinium, 1,4-dimethylpiperazinium, 1-n-butyl-piperidinium, 2-methylpiperidinium, 1-ethyl-2-methylpiperidinium, mono-, di- and triethanolammonium, ethyl diethanolammonium, n-butylmonoethanolammonium, tris(hydroxymethyl)methylammonium, phenyl-monoethanolammonium, and the like.

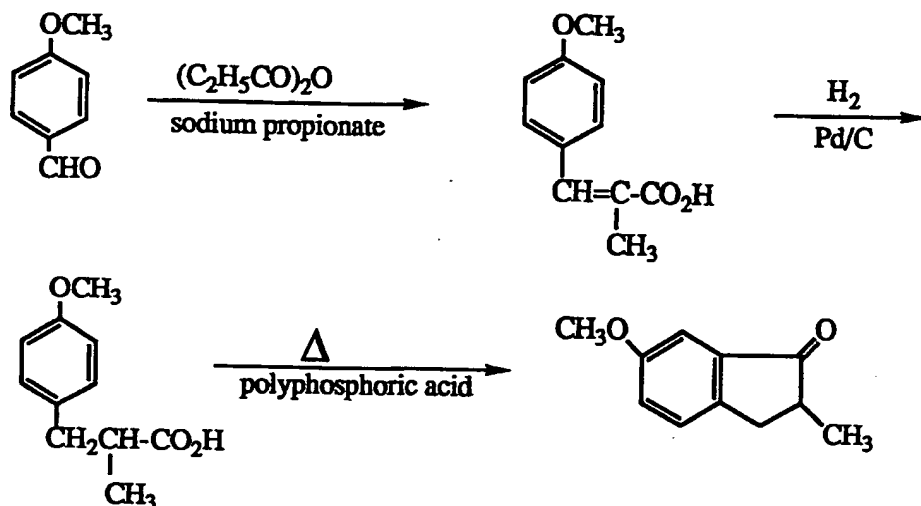
The compounds of the invention can be prepared by the following reaction schemes. When it is desired to prepare compounds having the formula



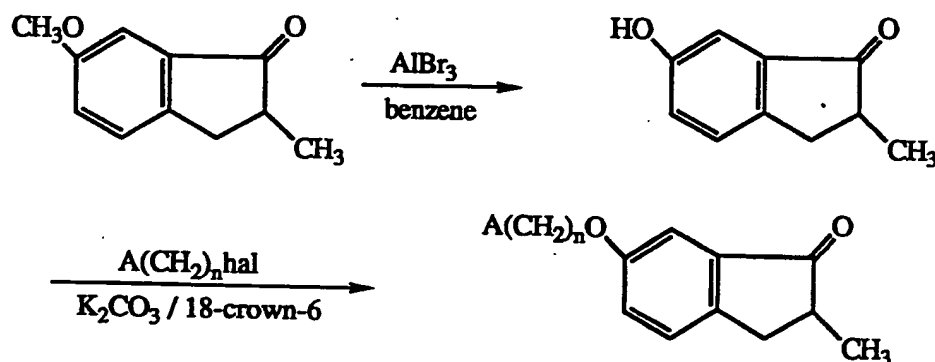
30

p-methoxybenzaldehyde, for example, is reacted with propionic anhydride, followed by reduction and ring closure to yield the intermediate 6-methoxy-2-methyl-1-indanone

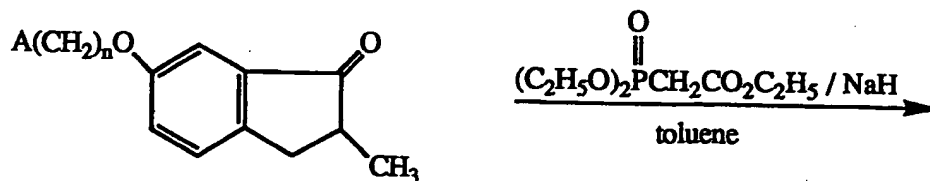
- 7 -



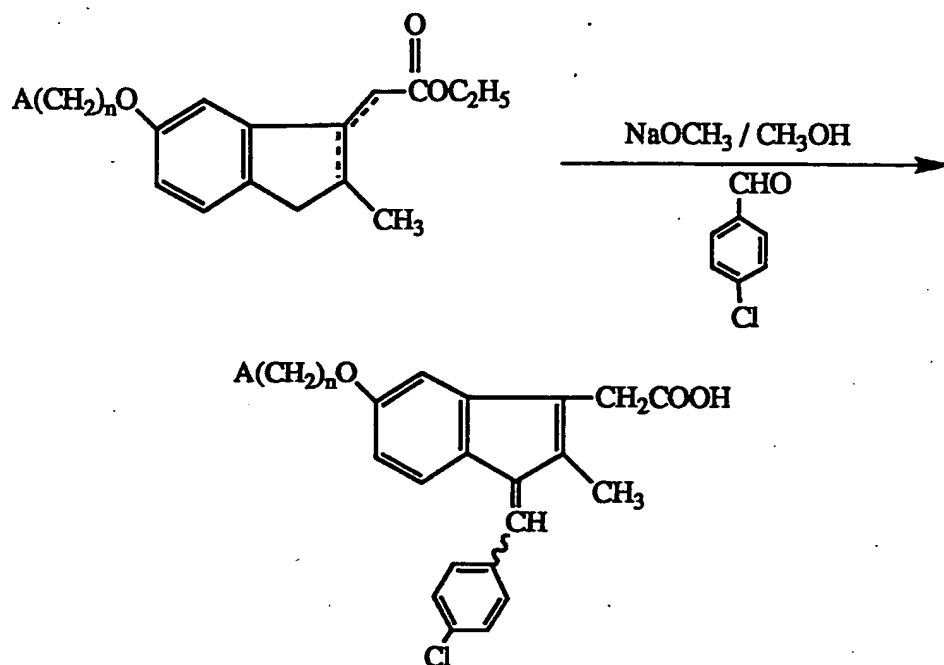
5 The indanone intermediate is then subjected to demethylation and the resulting hydroxy-indanone is reacted with an appropriate haloalkyl-A compound where A is as defined hereinbefore and hal is halo



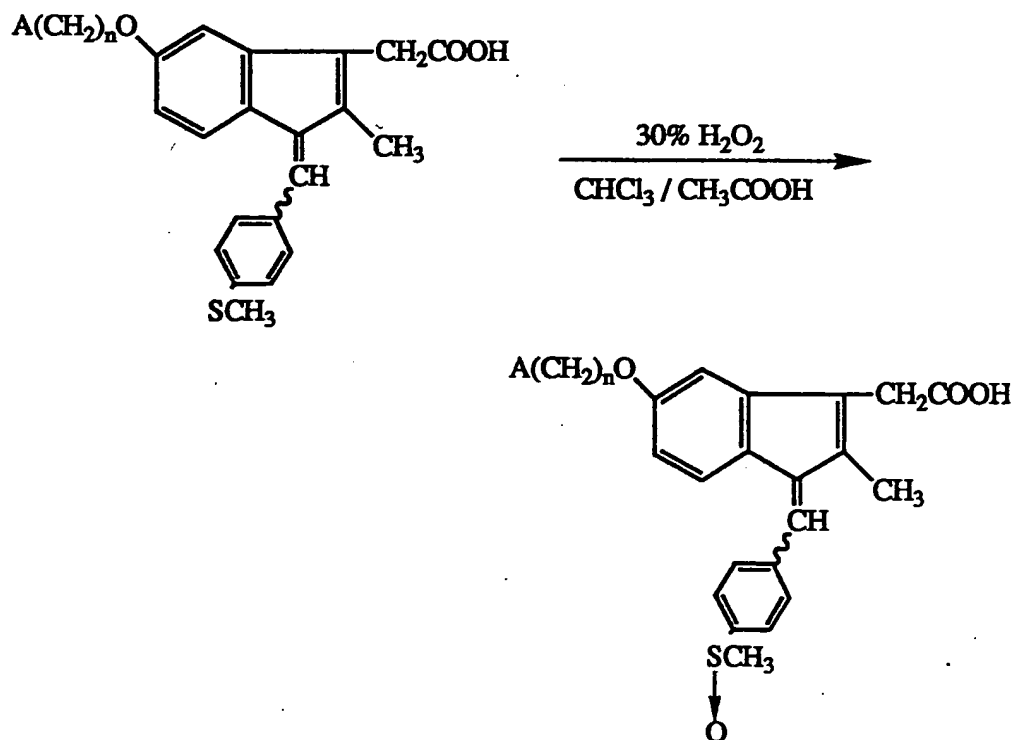
10 The latter intermediate, where $n=1$, is reacted with triethylphosphonoacetate in sodium hydride to yield an intermediate indene-3-acetic acid ethyl ester, which is then hydrolyzed and concomitantly reacted with an appropriate reactant to introduce the desired R^5 -methylene group onto the indene-3-acetic acid moiety, exemplified below by the introduction of a *p*-chlorophenylmethylene grouping



- 8 -

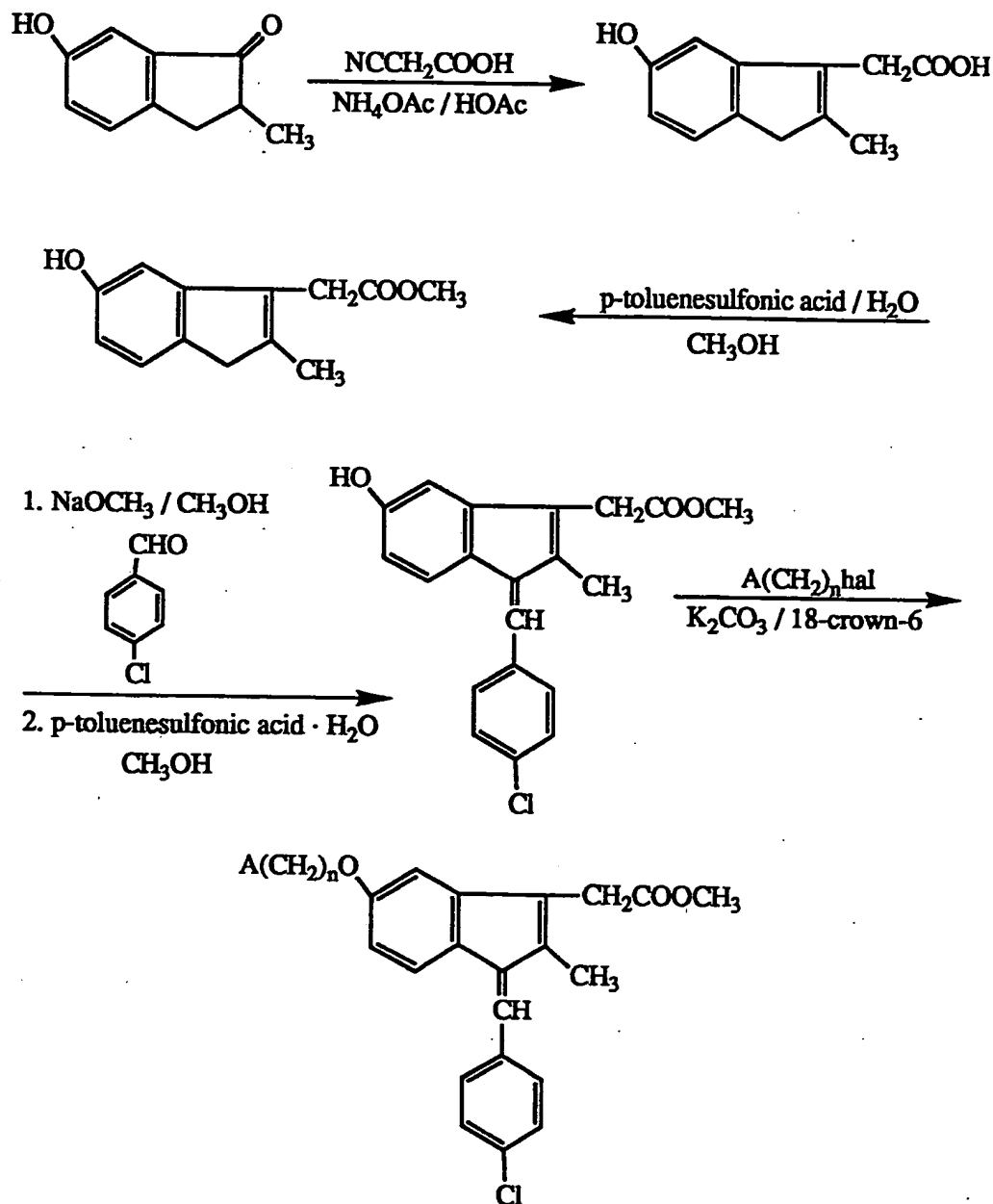


- Compounds in which the R^5 group is lower alkylthiophenyl can be prepared by using an appropriate loweralkylthiobenzaldehyde. The compounds in which R^5 is a lower-alkylsulfinylphenyl grouping can be prepared from the loweralkylthiophenyl-containing compounds by reaction with 30% H_2O_2 in chloroform/acetic acid.
- 5



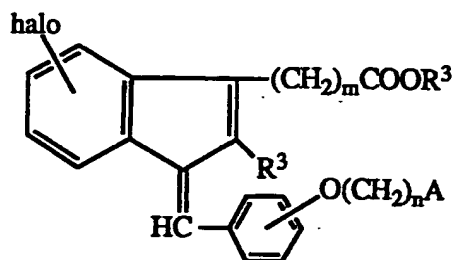
- 9 -

- In an alternative preparation scheme, the intermediate hydroxyindanone can be reacted with cyanoacetic acid to give the corresponding hydroxyindene-3-acetic acid, which is then esterified before introduction of the R⁵-methylene grouping in order to facilitate the purification of desired intermediates. Since introduction of the R⁵-methylene grouping is accompanied by ester hydrolysis, the intermediate free acid is re-esterified to facilitate purification followed by reaction with an appropriate halo-alkyl-A group to yield the desired final product
- 5

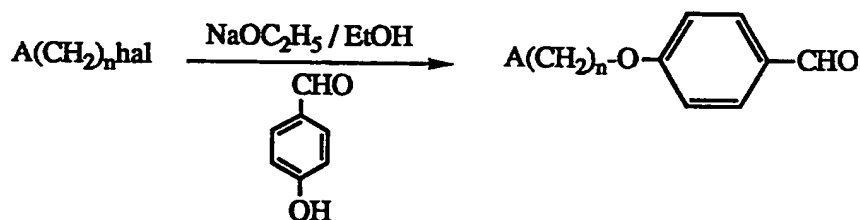


- 10 -

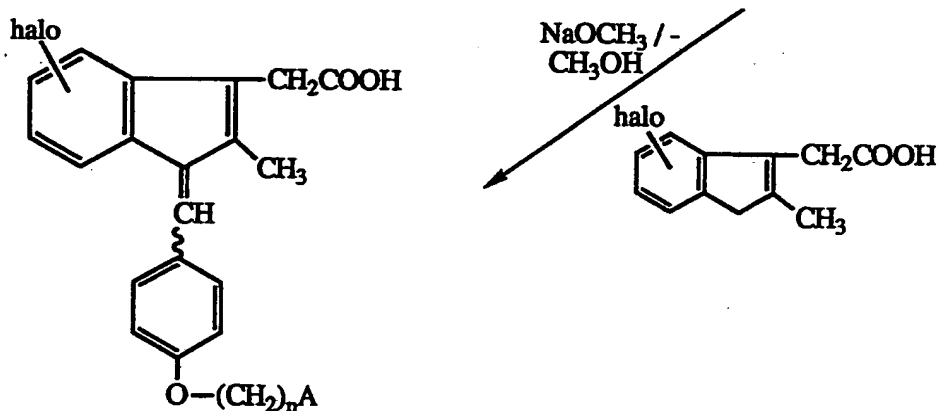
Compounds having the formula



can be prepared by reacting a halo-indene-3-acetic acid with a $A(CH_2)_n$ -containing benzaldehyde prepared from the corresponding individual components



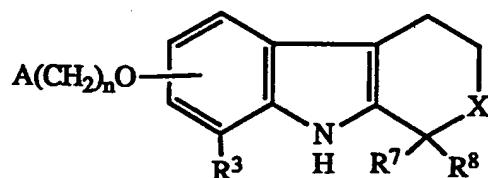
5



In all of the above-outlined reaction schemes, the final product free acids can be esterified via conventional methods and in like fashion, final product esters can be hydrolyzed by known procedures to yield the corresponding free acids.

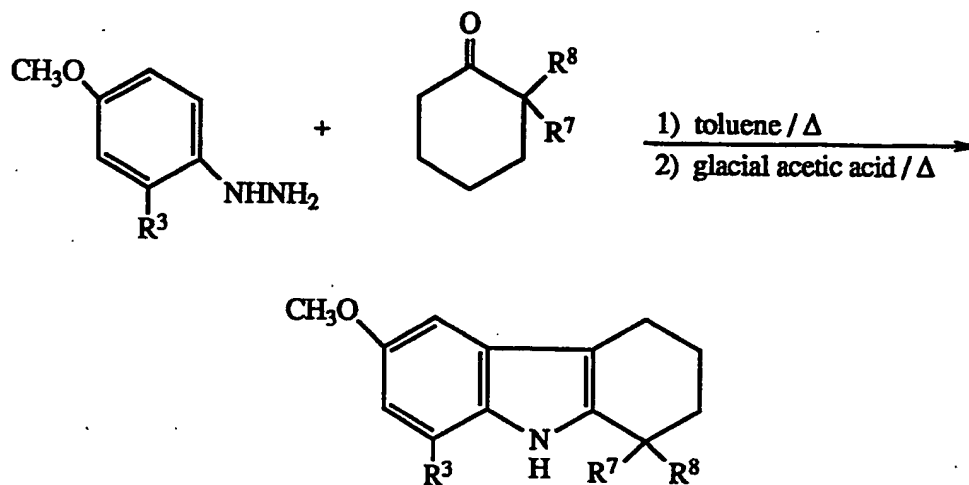
10

Compounds of the invention having the formula



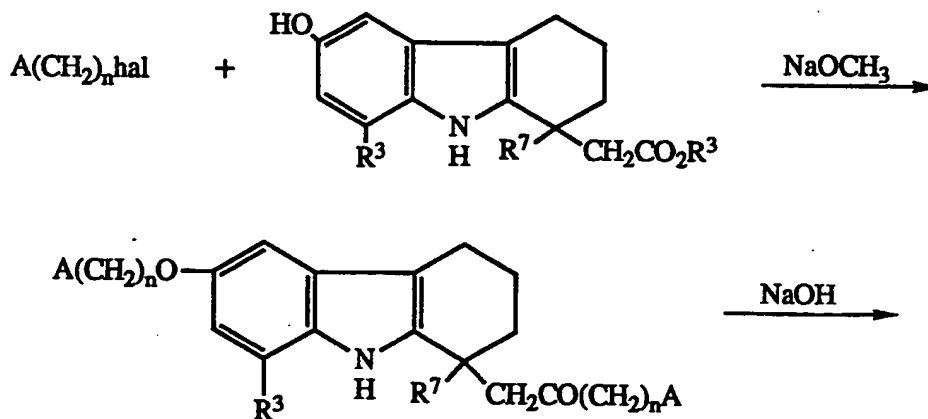
- 11 -

in which X is $-\text{CH}_2-$ can be prepared by initially reacting 4-methoxyphenylhydrazine with, for example, 2-carbomethoxymethyl-2-alkylcyclohexanone, followed by ring closure to yield an intermediate tetrahydro-methoxy-1H-carbazole-1-acetic acid



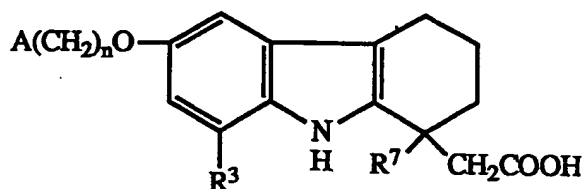
5

The latter intermediate is demethylated with hydrobromic acid to yield the corresponding hydroxy compound, which is then reacted with an appropriate halo-loweralkyl-A compound by one of several routes. In one such preparative sequence, two equivalents of the starting material, $\text{A}(\text{CH}_2)_n\text{hal}$, are reacted with a metal derivative of the hydroxycarbazole-1-acetic acid to form an intermediate ester ether which is hydrolyzed to yield the desired final products. The metal derivative of the hydroxycarbazole-1-acetic acid may be prepared by treating the acid with an alkali metal alkoxide, such as sodium methoxide.



15

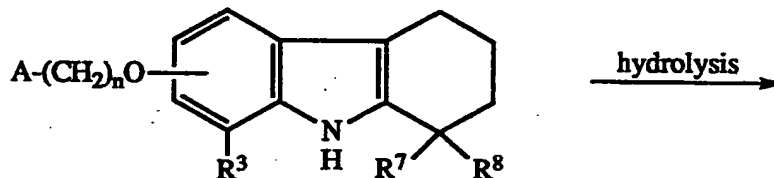
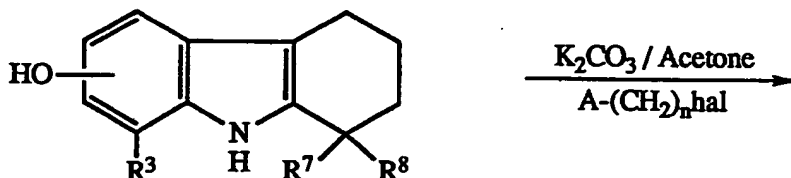
- 12 -



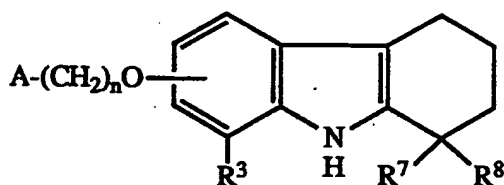
In the above sequence, A, n, m and R⁷ are as defined hereinbefore and hal denotes chloro, bromo or iodo.

5 In an alternative sequence, it is possible to use only one equivalent of starting material A(CH₂)_nhal with the metal derivative to obtain the desired final product directly, without proceeding through the ethyl ester intermediate.

In yet another reaction sequence, the desired final products can be prepared by the alkylation of alkyl esters of the hydroxycarbazole-1-acetic acid:

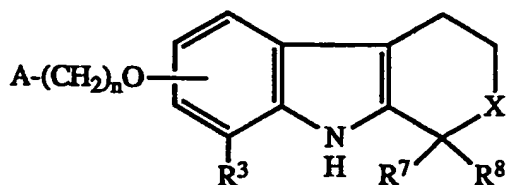


10



where A, n, m, R³, R⁷, R⁸ and hal are as defined hereinbefore. Hydrolysis is carried out using a dilute hydroxide, such as for example sodium hydroxide.

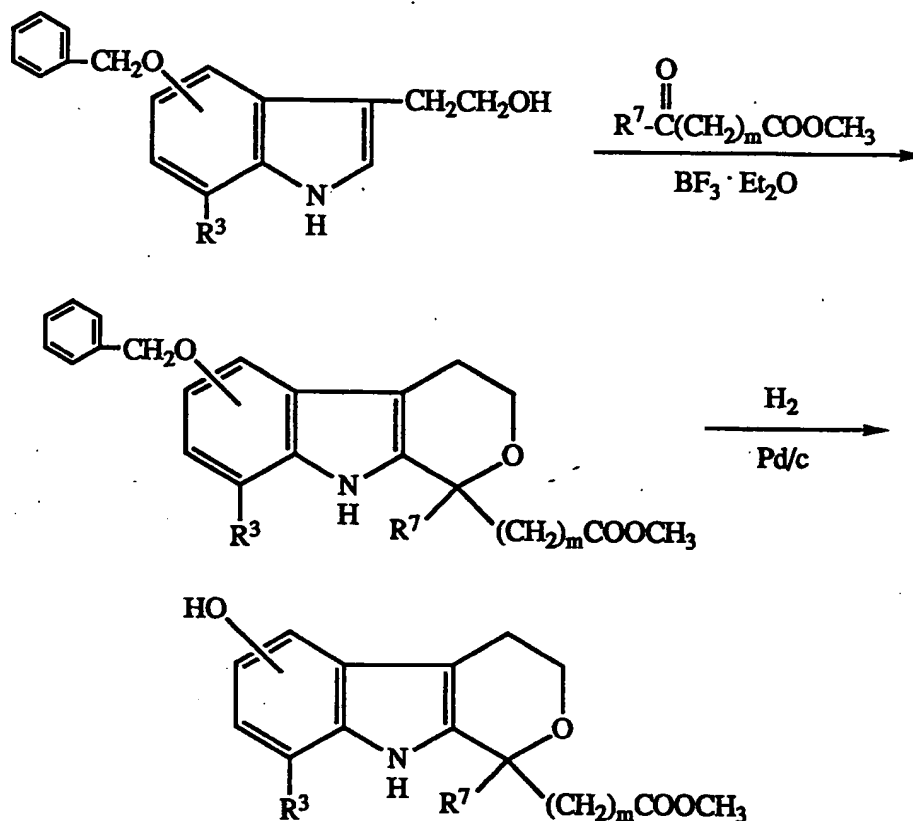
Compounds of the invention having the formula



15

- 13 -

- in which X is -O- can be prepared by the above-outlined reaction sequences which differ only in the preparation of the starting tetrahydro-6-hydroxypyrano[3,4-b]indole-1-lower alkanolic acid esters. The latter can be prepared by the reaction of, for example, a
- 5 5-benzyloxytryptophol with a loweralkyl-(R⁷-carbonyl)lower alkanolate in boron trifluoride etherate to yield an intermediate 1-R⁷-tetrahydro-6-(phenylmethoxy)pyrano[3,4-b]indole-1-alkanoic acid ester, which is then subjected to reduction to yield the corresponding 6-hydroxy ester

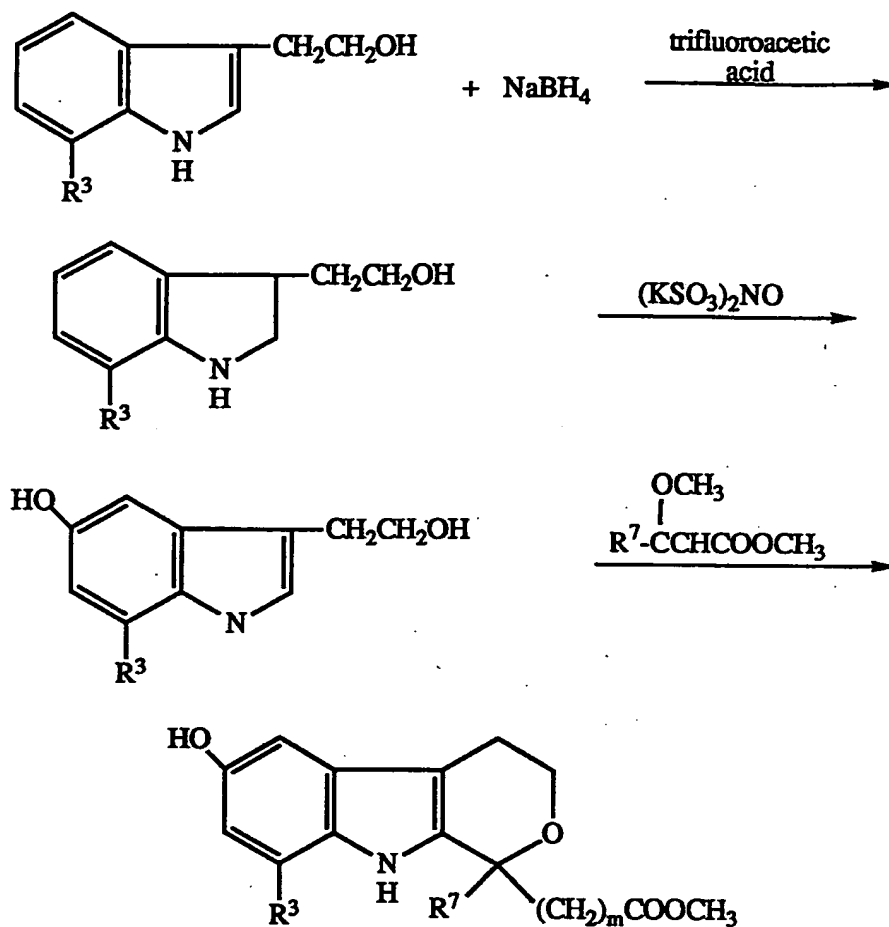


10

The latter intermediate can then be reacted as outlined earlier with an appropriate $A(CH_2)_n$ hal compound to yield the desired final compounds.

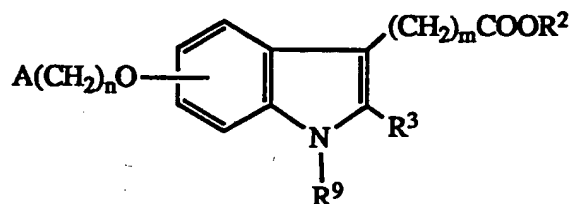
- Another scheme by which the starting tetrahydro-6-hydroxypyrano[3,4-b]indole 1-alkanoic acid ester can be prepared involves reducing 7-loweralkyltryptophol
- 15 to 7-loweralkyl-2,3-dihydrotryptophol, followed by reacting the latter with potassium nitrosodisulfonate to yield a 7-loweralkyl-5-hydroxytryptophol, which is then reacted with a suitable lower alkyl-3-methoxy-lower alkanolate to yield the desired intermediate tetrahydro-6-hydroxypyrano[3,4-b]indole-1-loweralkanoic acid ester

- 14 -



- 5 As with the previously described indene-1-acetic acid derivatives, the carbazole final product free acids can be esterified via conventional methods and in like fashion, final product esters can be hydrolyzed by known procedures to yield the corresponding free acids.

Compounds of the invention having, for example, the formula

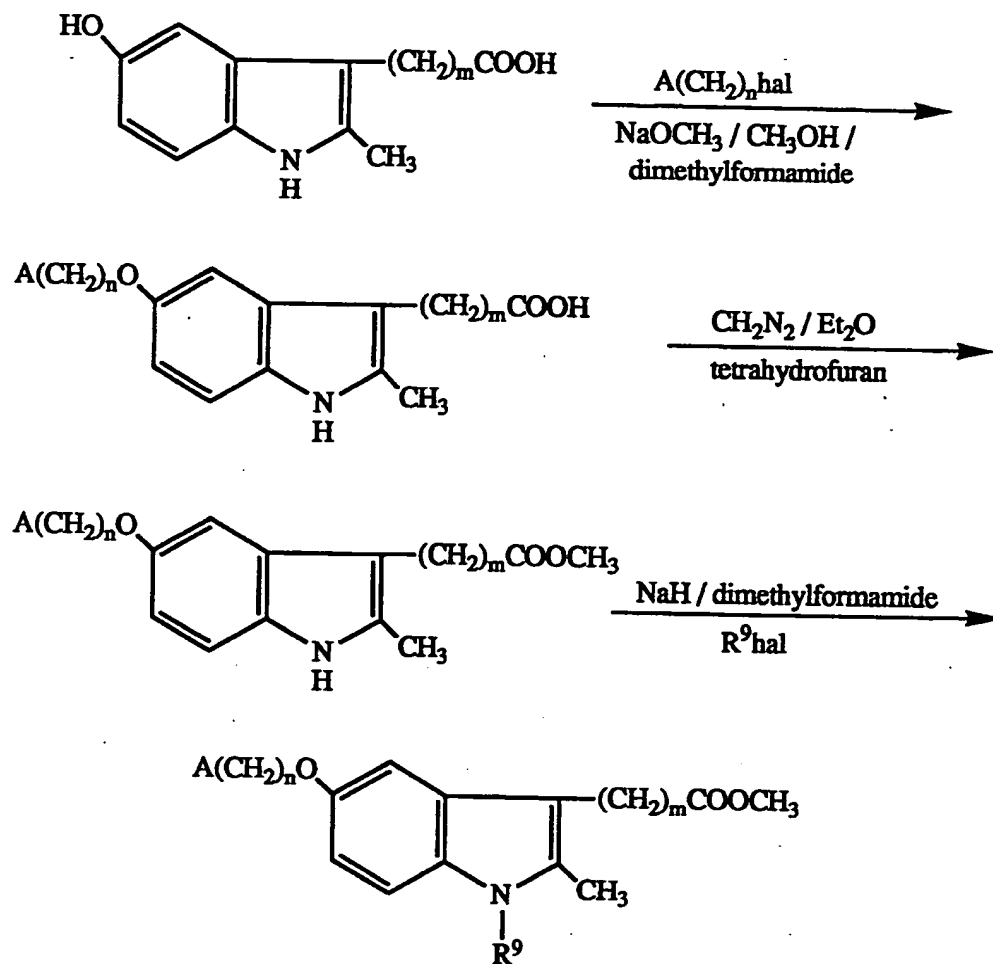


10

can be prepared by reacting 5-hydroxy-2-methyl-1H-indole-3-carboxylic acid with an appropriate A(CH₂)_nhal compound in the presence of sodium methoxide/methanol to yield the intermediate A(CH₂)_nO-containing indole alkanoic acid derivative, which is then esterified and reacted with a suitable substituted benzyl or benzoyl halide to yield

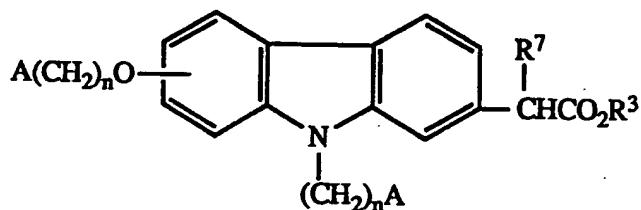
- 15 -

the desired final product in ester form, which can be converted to the free acid form by conventional methods.



5

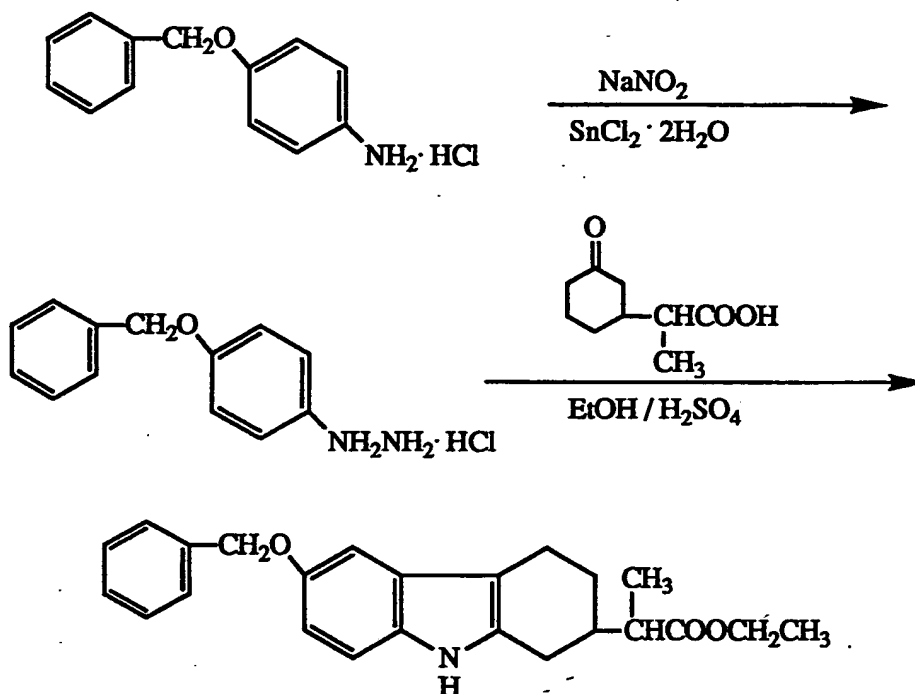
Compounds of the invention having the formula



10 can be prepared via the following reaction sequence: 4-benzyloxylaniline is reacted with sodium nitrite in the presence of stannous chloride to yield 4-benzyloxyhydrazine, which is reacted with α -methyl-3-oxocyclohexanone acetic acid to yield an intermediate

- 16 -

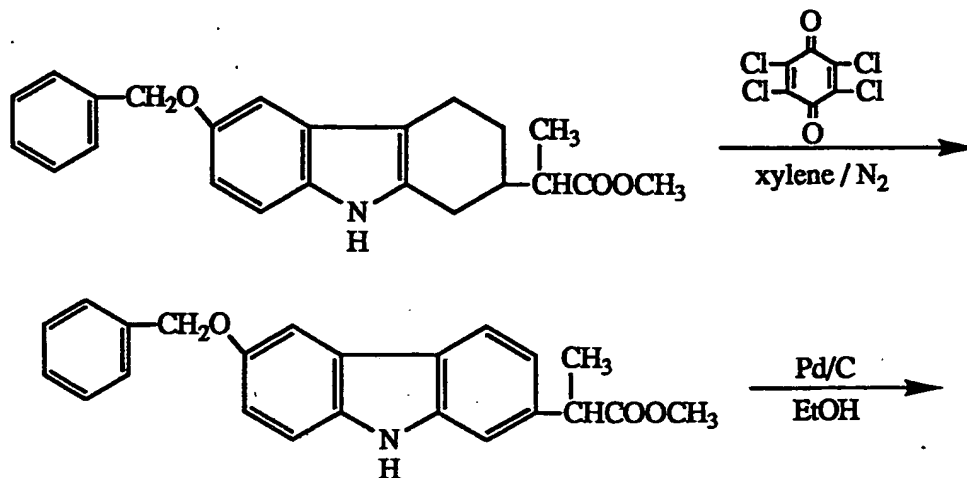
α -methyl-tetrahydrocarbazole acetic acid, which is esterified with ethanol to yield the intermediate ethyl ester.



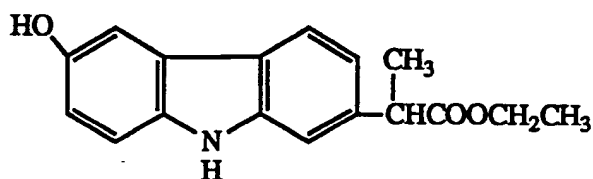
5

The α -methyl tetrahydrocarbazole acetic acid ester intermediate is reacted under reflux with chloranil in xylene under a nitrogen atmosphere to yield the corresponding α -methylcarbazole acetic acid, which is reduced by hydrogenation to remove the benzyloxy group, yielding the 6-hydroxy- α -methyl carbazole acetic acid ester intermediate.

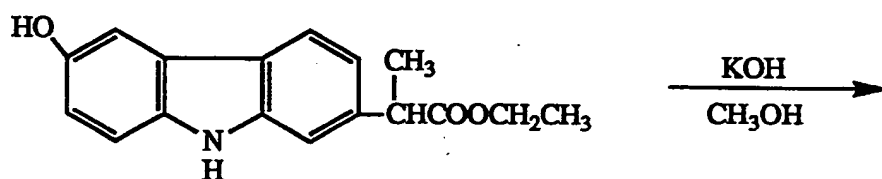
10



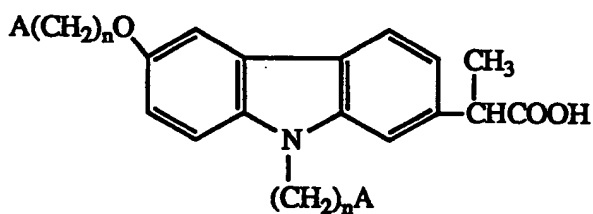
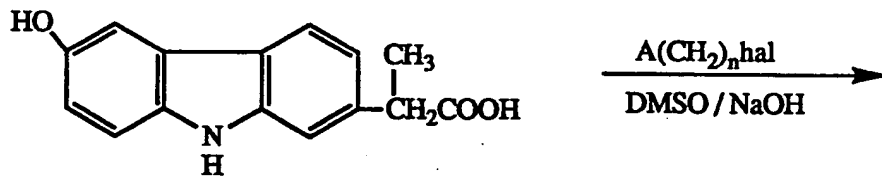
- 17 -



The latter intermediate is then hydrolyzed to give the free carboxylic acid intermediate, which is then reacted with an appropriate haloalkyl-A compound, where A is as hereinbefore defined and hal is halo, to yield the desired final product.

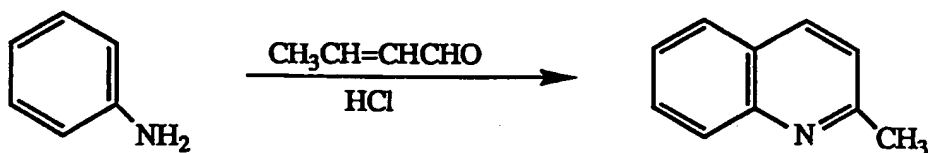


5

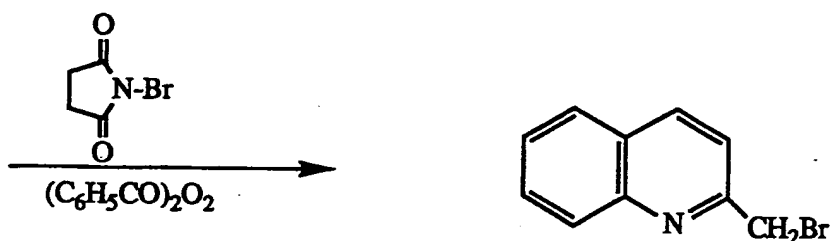


The conventional starting materials used in the reaction sequences outlined above are available commercially or can be prepared by methods known in the art. Thus, for example, the intermediate compound 2-bromomethylquinoline can be prepared by the following reaction sequence:

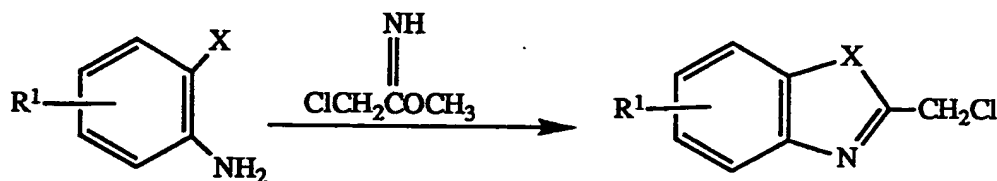
10



- 18 -



The benzo-fused heterocyclic compounds used in the above reaction sequences are also either commercially available or can be prepared by methods conventional in the art. Thus, for example, such intermediates as 1-methyl-2-chloromethylbenzimidazole, 2-chloromethylbenzthiazole and 2-chloromethylbenzoxazole can be prepared by the following reaction scheme



wherein X is O , S or NCH_3 . The reaction is preferably carried out at a controlled low temperature in an organic solvent, such as methylene chloride.

Certain compounds within the scope of the invention exist in the form of *E* and *Z* stereoisomers and the individual isomers can be differentiated by the prefixes *E* and *Z*, as assigned by the accepted sequence rules procedures. Accordingly, the present invention embraces the *E*, *Z* and mixed isomer forms of those final product compounds exhibiting this form of stereoisomerism.

The compounds of the invention, by virtue of their ability to inhibit the activity of PLA_2 enzyme, as well as that of lipxygenase enzyme and to antagonize mediators arising from the enzymatic pathway, are useful in the treatment of conditions mediated by products of the oxidation of arachidonic acid. Accordingly, the compounds are indicated in the treatment of such diseases as rheumatoid arthritis, inflammatory bowel disease, osteoarthritis, tendinitis, bursitis, psoriasis (and related skin inflammation) and similar conditions involving inflammation. Moreover, by virtue of their ability to antagonize the effect of LTC_4 , LTD_4 and LTE_4 , which are the constituents of SRS-A , they are useful for the inhibition of symptoms induced by these leukotrienes. Accordingly, the compounds are indicated in the prevention and treatment of those disease states in which LTC_4 , LTD_4 and LTE_4 are causative factors, for example allergic rhinitis, allergic bronchial asthma and other leukotriene mediated nasobronchial obstructive air-passageway conditions, as well as in other immediate hyper-

sensitivity reactions, such as allergic conjunctivitis. The compounds are especially valuable in the prevention and treatment of allergic bronchial asthma.

The compounds of the invention are cytoprotective agents and are considered especially useful when administered with conventional non-steroidal anti-inflammatory drugs, whose major side effect is gastrointestinal irritation. The cytoprotective effect of the compounds of the invention significantly reduces the gastro-irritant impact of conventional anti-inflammatory drugs. This effect is based not only on the ability of the compounds of the invention to inhibit the biological effects of leukotrienes and/or control the biosynthesis of these substances, as by inhibiting lipooxygenase, but also by a shunting effect, whereby the control of the lipooxygenase pathway "shunts" the oxidation of arachidonic acid into the cyclooxygenase pathway, giving rise to an increase in the formation of cytoprotective prostaglandins. These biological effects make the compounds of the invention especially useful in treating such conditions as erosive esophagitis, inflammatory bowel disease and induced hemorrhagic lesions such as those induced by alcohol or non-steroidal anti-inflammatory drugs (NSAID's), hepatic ischemia, noxious agent induced damage or necrosis of hepatic, pancreatic, renal or myocardial tissue; liver parenchymal damage caused by hepatotoxic agents such as carbon tetrachloride and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt-induced pancreatic or gastric damage; trauma or stress-induced cell damage; and glycerol-induced renal failure.

When the compounds of the invention are employed in the treatment of allergic airway disorders, as anti-inflammatory agents and/or as cytoprotective agents, they can be formulated into oral dosage forms such as tablets, capsules and the like. The compounds can be administered alone or by combining them with conventional carriers, such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, low melting wax, cocoa butter and the like. Diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet-disintegrating agents and the like may be employed. The compounds may be encapsulated with or without other carriers. In all cases, the proportion of active ingredients in said compositions both solid and liquid will be at least to impart the desired activity thereto on oral administration. The compounds may also be injected parenterally, in which case they are used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic. For administration by inhalation or insufflation, the compounds may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol.

- 20 -

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until
5 the optimum effect under the circumstances is reached. In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects, and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

10 The PLA₂ and lipoxxygenase inhibitory and leukotriene antagonist effects, as well as the anti-inflammatory and potential gastroirritant effects of the compounds of the invention, may be demonstrated by standard pharmacological procedures which are described more full in the examples given hereinafter.

These procedures, inter alia, determine the specificity of action of the
15 compounds of the invention as PLA₂ inhibitors as measured by their ability to inhibit the synthesis of LTB₄ and PGE₂ by rat glycogen-elicited polymorphonuclear leukocytes, as well as measure their ability to inhibit arachidonic acid release mediated by human and non-human source PLA₂. The procedures further measure the ability of the compounds of the invention to inhibit, in vivo, the activity of exogenously
20 administered PLA₂. The pharmacological testing additionally demonstrates the ability of the compounds of the invention to inhibit, in vivo, the lipoxxygenase and cyclooxygenase pathways of arachidonic acid metabolism; the in vitro, leukotriene antagonist activity of the compounds of the invention; and also measures the in vivo activity of the compounds as anti-inflammatory agents in the rat carrageenan paw edema assay.
25 Finally, the potential of the compounds to induce acute gastroirritation in rats is measured in a test procedure.

The following examples show the preparation and pharmacological testing of compounds within the invention.

- 21 -

Example 1

**3-[(4-Chlorophenyl)methylene]-[2-methyl-6-(2-quinolinyl-
methoxy)]-3H-indene-1-acetic acid**

A. p-Methoxy- α -methyl cinnamic acid

- 5 A mechanically stirred mixture of 4-methoxybenzaldehyde (47.6 g, 0.35 mole), propionic anhydride (78.3 g, 0.602 mole) and sodium propionate (33.5 g, 0.35 mole) is placed under nitrogen in an oil bath heated at 150°C for 15 hours. Upon addition of water (130 mL) under vigorous stirring a yellow solid is obtained. It is redissolved in 2N-KOH (pH 11) and the solution is extracted with ether.
- 10 The aqueous phase is acidified (ice bath) with concentrated HCl. The white solid is collected, washed with water and dried to provide the title compound (47.69 g, 71%, m.p. 153-154°C).

NMR (DMSO- d_6 , 400 MHz): δ 2.01 (d, J 1.34 Hz, 3H, 2-CH₃), 3.77 (s, 3H, OCH₃), 6.98 (d, J 8.81 Hz, 2H, ArH), 7.43 (d, J 8.7 Hz, ArH), 7.53 (s, 1H, ArCH=C).

MS (EI, m/z): 192 (b.p., M)⁺.

Analysis for: C₁₁H₁₂O₃.

Calculated: C, 68.74; H, 6.29.

Found: C, 68.80; H, 6.43.

20 B. p-Methoxy- α -methyl hydrocinnamic acid

A mixture of the acid (44 g, 0.229 mole) of Step A, and 10% Pd/C (4.4 g) in dry methanol (500 mL) is hydrogenated overnight at 50 psi. The mixture is filtered (Solka-Floc) and the filtrate evaporated to dryness to yield a pale yellow oil, which is used without further purification (44.5 g).

- 25 NMR (CDCl₃, 400 MHz): δ 1.16 (d, J 6.9 Hz, 3H, 2-CH₃), 2.62 (dd, 1H, ArCH) and 2.70 (m, 1H, ArCH), 3.00 (dd, 1H, CH), 3.78 (s, 3H, OCH₃), 6.82 (d, 2H, ArH), 7.09 (d, 2H, ArH).

MS (EI, m/z): 194 (M)⁺, 121 (b.p.).

C. 6-Methoxy-2-methyl-1-indanone

- 30 A mechanically stirred mixture of the crude propionic acid (44 g, 0.227 mole) of Step B, is added to warm (50°C) polyphosphoric acid (420 g). The mixture is then placed in an oil bath heated at 95°C for 90 minutes (TLC, 9:1 dichloromethane-methanol, UV). The warm mixture is poured into water (3 L) and stirred overnight at room temperature. It is then extracted with ether and ethyl acetate

- 22 -

and the combined extracts are washed with saturated NaHCO_3 to neutral. The organic phase is washed with brine and dried (MgSO_4). Removal of the solvent provides the title compound as an amber oil. It is purified by flash chromatography (on silica Merck-60, dichloromethane as eluent) to yield 25.58 g (64%) of a pale yellow oil.

5 NMR (CDCl_3 , 400 MHz): δ 1.31 (d, J 7.4 Hz, 3H, 2- CH_3), 2.65 (dd, 1H, ArCH) and 2.74 (m, 1H, ArCH), 3.32 (dd, 1H, CH), 3.83 (s, 3H, OCH_3), 7.20 (m, 2H, ArH), 7.34 (d, 1H, ArH).

MS (EI, m/z): 176 (M)⁺, 161 (b.p., M- CH_3)⁺.

D. 6-Hydroxy-2-methyl-1-indanone

10 To a stirred solution of anhydrous aluminum bromide (69.82 g, 0.261 mole) in anhydrous benzene (250 mL) kept under nitrogen is added dropwise over 30 minutes a solution of the methoxy indanone (18 g, 0.102 mole) of Step C, in benzene (60 mL). The mixture is gently refluxed for 3 hours (TLC, dichloromethane-ethyl acetate 8:2, UV), cooled in an ice bath and treated dropwise with 6N-HCl (ca.
15 200 mL) to decompose the aluminum complex. The aqueous phase is extracted with ether (3 times), the extracts are concentrated at reduced pressure and extracted with 2.5N-NaOH (2x75 mL and 1x50 mL). The basic extracts are neutralized (ice bath) with concentrated HCl and the oil that separates is extracted with ether (3 times). The combined extracts are washed with brine, dried (MgSO_4) and evaporated to yield an oil
20 that readily solidifies. The crude material is flash chromatographed (on silica Merck-60, gradient CH_2Cl_2 , CH_2Cl_2 -ethyl acetate 85:15) to provide the pure title compound (13.60 g, nearly colorless solid, 82%).

NMR (CDCl_3 , 400 MHz): δ 1.31 (d, J 7.44 Hz, 3H, 2- CH_3), 2.65 (dd, 1H, ArCH) and 2.76 (m, 1H, ArCH), 3.32 (dd, 1H, CH), 6.68 (s, 1H, OH), 7.18 (dd,
25 1H, ArH), 7.30 (m, 2H, ArH).

MS (EI, m/z): 162 (M)⁺, 147 (b.p., M- CH_3)⁺, 133 (M- C_2H_5)⁺.

E. 6-(2-Quinolinylmethoxy)-2-methyl-1-indanone

A mixture of the phenol (15.16 g, 93.58 mmole) of Step D, powdered anhydrous potassium carbonate (12.93 g, 93.6 mmole), 18-crown-6 (2.47 g,
30 9.36 mmole) and dry acetonitrile (200 mL) is stirred at room temperature under a nitrogen for 15 minutes. 2-Chloromethylquinoline (free base, freshly prepared from 18.29 g or 102.96 mmole of the hydrochloride salt) is added in one portion and the mixture is placed in an oil bath heated at 65°C for 11 hours (TLC, dichloromethane-methanol 9:1, UV). The solvent is removed in vacuo and the residue is partitioned
35 between ethyl acetate and water. The organic phase is washed with brine, dried

- 23 -

(MgSO₄) and evaporated to yield an oil which solidifies upon trituration with hexane (ca. 31 g). The crude product is purified by flash chromatography (on silica Merck-60, absorbed in methylene chloride, eluted with CH₂Cl₂-ethyl acetate 90:10 and 85:15) to provide 5.95 g of slightly impure material together with 24.55 g of the pure title compound (pale yellow solid, 84.8%).

NMR (CDCl₃, 400 MHz): δ 1.29 (d, J 7.36 Hz, 3H, 2-CH₃), 2.65 (dd, 1H, ArCH) and 2.73 (m, 1H, ArCH), 3.32 (dd, 1H, CH), 5.41 (s, 2H, ArCH₂O), 7.3-7.38 (m, 3H, ArH), 7.55 (t, J ca. 7 Hz, 1H, ArH), 7.64 (d, J 8.5 Hz, 1H, ArH), 7.74 (t, J ca 7 Hz, 1H, ArH), 7.83 (d, J 8 Hz, 1H, ArH), 8.11 (d, J 8.4 Hz, 1H, ArH), 8.20 (d, J 8.4 Hz, 1H, ArH).

MS (EI, m/z): 303 (M)⁺, 142 (b.p., C₁₀H₈N)⁺, 115.

F. 2-Methyl-5-(2-quinolinylmethoxy)-indene-3-acetic acid ethylester

Triethylphosphonoacetate (22.41 g, 100 mmole) is added dropwise under nitrogen to a stirred and cooled (0°C) slurry of NaH (57% in oil, 4.27 g, 100 mmole) in dry toluene (250 mL). The cooling bath is removed and stirring continued at room temperature for 60 minutes whereby an almost homogeneous solution is obtained. A solution of the indanone (15.15 g, 50 mmole) of Step E, in toluene (50 mL) is then added dropwise. The flask is placed in an oil bath heated at 95°C for 19 hours (TLC, traces of starting material present, dichloromethane-ethyl acetate 9:1, UV, Vaughn's). The reddish solution is cooled, diluted with water and extracted with ethyl acetate (3 times). The combined extracts are washed with brine, dried (anhydrous K₂CO₃) and evaporated to dryness. The residue (heavy brown oil) is flash chromatographed (on silica Merck-60, eluted using a gradient dichloromethane → dichloromethane:ethyl acetate 84:16) to provide the title compound as a mixture of endo and exo isomers (16.3 g, 87.4%, oil that solidifies upon standing) together with unreacted, more polar starting material (1.84 g, 12% recovery).

MS (EI, m/z): 373 (M)⁺, 344 (M-C₂H₅)⁺, 300 (M-COOC₂H₅)⁺, 143 (b.p.), 115.

G. 3-[(4-Chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid

To a vigorously stirred mixture of the ester (mixture of isomers, 6.9 g, 18.5 mmole) prepared as described in Step F, and p-chlorobenzaldehyde (2.86 g, 20.3 mmole, 1.1 equiv.) in dry methanol (45 mL) is added dropwise under nitrogen 25% methanolic sodium methoxide (8 mL, 2 equiv.). The mixture is warmed until it becomes homogeneous (ca. 65°C, bath temp.) and then refluxed for a total of 13 hours. After overnight at room temperature, the slurry (bright yellow precipitate) is treated

- 24 -

dropwise with water (35 mL) and a little methanol and refluxing is continued for another 4 hours (reaction followed by TLC). The dark orange solution is cooled, the methanol evaporated, more water added and the gelatinous precipitate is collected, washed with water and dried to provide the sodium salt of the title compound as a bright yellow solid. The latter is slurried in water and neutralized (to pH 6-6.5) with 10% acetic acid. The mixture is extracted with ethyl acetate (large volume), the extract is washed with brine and evaporated to dryness. The residue is azeotroped with benzene to provide an orange solid [7.52 g, mixture of Z (major) and E (minor) isomers]. This material is slurried in ether, stirred for 30 minutes, filtered and dried (4.32 g). The solid is extracted portionwise with hot ethyl acetate (containing some methanol and dichloromethane) until almost completely dissolved. The filtrate is concentrated in vacuo until precipitation occurs, diluted with ether and the yellow solid collected and dried (3.1 g, m.p. 218-220°C). Concentration of the mother liquors provides additional product (1.1 g, m.p. 200-203°C). Combined yield is 4.4 g (51%). The NMR spectrum is consistent [see: Shuman et al., J. Org. Chem., **42**, 1914, (1977)] with the Z-isomer.

NMR (DMSO- d_6 , 400 MHz): δ 2.11 (s, 3H, CCH₃), 3.54 (s, 2H, CH₂COO), 5.326 (s, 2H, OCH₂Ar), 6.60 (dd, 1H ArH), 6.95 (d, J 2.35 Hz, 1H), 7.14 (m, 2H, ArH), 7.52 (m, 4H, ArH), 7.60 (t, J 7.03 Hz, 1H, ArH), 7.66 (d, J 8.39 Hz, 1H, ArH), 7.77 (t, 1H, ArH), 7.99 (m, 2H, ArH), 8.4 (d, J=8.9 Hz, 1H, ArH).

UV (λ max, MeOH, nm): 232 (ϵ 39,594), 285.2 (14,830), 287.8 (14,921), 288 (14,921), 338.2 (10,839).

MS (+FAB, m/z): 468 (1Cl, M+H)⁺, 237, 131, 91 (b.p.).

Analysis for: C₂₉H₂₂ClNO₃

Calculated: C, 74.43; H, 4.74; N, 2.99.

Found: C, 74.54; H, 4.67; N, 3.13.

Example 2

2-Methyl-3-[[4-(methylthio)phenyl]methylene]-6-(2-quinolinylmethoxy)-3H-indene-1-acetic acid

To a vigorously stirred mixture of the ester (mixture of isomers, 6.7 g, 17.96 mmole), prepared as described in Example 1, Step F, and (4-methylthio)benzaldehyde (3.05 g, 19.06 mmole, 1.1 equiv.) in dry methanol (75 mL) is added dropwise under nitrogen 25% methanolic sodium methoxide (7.7 mL, 2 equiv.). The mixture is warmed until it becomes homogeneous (ca. 65°C, bath temp.).

- 25 -

and then refluxed for a total of 13 hours (TLC, CH₂Cl₂-ethyl acetate 9:1). After overnight at room temperature, the slurry (bright yellow precipitate) is treated dropwise with water (65 mL) and a little methanol and refluxing is continued for another 5.5 hours (reaction followed by TLC). The brown solution is cooled, the methanol evaporated, more water added and the gelatinous precipitate is collected, washed with water and dried to provide the sodium salt of the title compound as a yellow solid. The latter is slurried in water and neutralized (to pH 6-6.5) with 10% acetic acid. The mixture is extracted with ethyl acetate (large volume), the extract is washed with brine and evaporated to dryness. The residue is azeotroped with benzene to provide a yellow solid (4.47 g, 52%). This material is slurried in ether, stirred for 30 minutes, filtered and dried (4.13 g, m.p. 205-207°C, dec.). The solid is extracted portionwise with hot ethyl acetate (containing some methanol and dichloromethane) until almost completely dissolved. The filtrate is concentrated *in vacuo* until precipitation occurs and diluted with ether. The yellow solid is collected and dried (3.5 g, 35.4%, m.p. 207-209°C, dec.). The NMR spectrum is consistent [see: Shuman et al., *J. Org. Chem.*, **42**, 1914, (1977)] with the Z-isomer.

NMR (DMSO-d₆, 400 MHz): δ 2.11 (s, 3H, CCH₃), 2.51 (s, 3H, SCH₃), 3.53 (s, 2H, CH₂COO), 5.32 (s, 2H, OCH₂Ar), 6.60 (dd, 1H, ArH), 6.95 (d, 1H, J 2.35 Hz), 7.13 (s, 1H, ArH), 7.30 (m, 3H, ArH), 7.47 (d, 2H, J 8.4 Hz, ArH), 7.60 (t, J 7.0 Hz, 1H, ArH), 7.66 (d, 1H, J 8.49 Hz, ArH), 7.77 (t, 1H, J ca. 7 Hz, ArH), 7.99 (m, 2H, ArH), 8.4 (d, 1H, J 8.49 Hz, ArH).

UV (λ max, MeOH, nm): 231.5 (ϵ 37,382), 303 (9,739), 307.5 (9,342), 315 (10,525), 352.5 (13,407).

MS (+FAB), m/z: 480 (M+H)⁺.

Analysis for: C₃₀H₂₅NO₃S
Calculated: C, 75.13; H, 5.25; N, 2.92.
Found: C, 75.30; H, 5.25; N, 2.95.

Example 3

2-Methyl-3-[[[(4-methylsulfinyl)phenyl]methylene]-6-(2-quinolylmethoxy)-3H-indene-1-acetic acid monohydrate

A slurry of the thioether (1.67 g, 3.48 mmole) of Example 2 in a cold mixture of chloroform and glacial acetic acid (65:35, 40 mL) is treated dropwise (via syringe) with 30% H₂O₂ (0.403 mL). The mixture is stirred for 30 minutes in the cold and then at room temperature for 24 hours. A clear solution is obtained after 2 hours and a small amount of H₂O₂ is added after 4 and 7 hours, respectively, to drive the

- 26 -

- reaction to completion (reaction followed by TLC, aliquot treated with water and extracted with ethyl acetate). The chloroform is evaporated, the residue is diluted with water and neutralized in the cold with the calculated amount of NH_4OH . The precipitate is filtered, slurried in water, collected, washed with water and dried in vacuo (over P_2O_5) to yield the crude acid as a yellow solid. The solid is redissolved in a large volume of warm (30-35°C) ethyl acetate (containing some methanol and dichloromethane) and filtered. The filtrate is concentrated in vacuo until precipitation starts and diluted with ether. The precipitate is collected, washed with ether and dried (fluffy solid, m.p. 136-137°C, sintering and foaming).
- 10 NMR (DMSO-d_6 , 400 MHz): δ 2.12 (s, 3H, 2- CH_3), 2.80 (s, 3H, SOCH_3), 3.55 (s, 2H, CH_2COO), 5.32 (s, 2H, ArCH_2O), 6.58 (dd, 1H, ArH), 6.96 (d, J 2.3 Hz, 1H), 7.14 (d, J 8.36 Hz, 1H, ArH), 7.21 (s, 1H, ArH), 7.58-7.80 (m 7H, ArH), 7.98 (m, 2H, ArH), 8.39 (d, J 8.5 Hz, 1H, ArH), 12.36 (s, 1H, COOH).
- 15 MS (+FAB, m/z): 518 ($\text{M}+\text{Na}$)⁺, 496 ($\text{M}+\text{H}$)⁺.
- Analysis for: $\text{C}_{30}\text{H}_{25}\text{NO}_4\text{S} \cdot \text{H}_2\text{O}$
- Calculated: C, 70.19; H, 5.30; N, 2.73.
- Found: C, 69.15; H, 4.93; N, 2.65.

Example 4

20 5-Fluoro-2-methyl-1-[[4-(2-quinolinylmethoxy)-phenyl]methylenel-1H-indene-3-acetic acid

- A. 4-[(2-quinolinyl)-methoxy]-benzaldehyde
- To a solution of sodium metal (0.9 g, 39.13 g.a.) in absolute ethanol (50 mL) is added dropwise under nitrogen a solution of 4-hydroxybenzaldehyde (5 g, 40.94 mmole) in absolute ethanol (50 mL). The mixture is gently refluxed for 1 hour and then treated dropwise with a solution of 2-chloromethylquinoline (free base, 7.24 g, 40.76 mmole), freshly prepared from the HCl salt) in ethanol (50 mL). The mixture is refluxed for 24 hours, the solvent is evaporated and the residue is partitioned between water and ethyl acetate. The organic layer is washed with 5% NaOH (pH 8), water, brine to neutral and dried (MgSO_4). Removal of the solvent yields the title compound as a yellow solid (9.81 g). The crude material is further purified by flash chromatography (on silica Merck-60, hexane-ethyl acetate 9:1 to remove less polar impurities and 8:2 to elute the product). Yield: 7.37 g (71.5%), m.p. 82-83°C.
- 30 NMR (CDCl_3 , 200 MHz): δ 5.5 (s, 2H, ArCH_2O), 7.2-8.6 (m, 9H, ArH), 9.80 (s, 1H, CHO).
- 35

- 27 -

B. 5-Fluoro-2-methyl-1-[[4-(2-quinolinylmethoxy)phenyl]methylene]-1H-indene-3-acetic acid

To a mixture of 5-fluoro-2-methyl-indene-3-acetic acid (prepared according to the procedure disclosed in U.S. 3,654,349) (2 g, 9.7 mmole) and the aldehyde (3.2 g, 12.19 mmole) of Step A, in dry methanol (40 mL) is added dropwise under nitrogen 25% methanolic sodium methoxide (6.48 mL). The mixture is warmed until homogeneous and then refluxed for a total of 16 hours. The solvent is evaporated and the residue is slurried in water. The gelatinous precipitate is collected, washed with water and dried. It is then slurried in ether, filtered and dried to provide the sodium salt of the title compound as a yellow solid (2.03 g, 46.3%). The salt is slurried in water and neutralized (to pH 6-6.5) with 10% acetic acid. The acid is extracted with ethyl acetate (large volume), dried (MgSO₄) and evaporated to dryness. The crude acid is recrystallized from a hot mixture of methanol and ethanol (large volume needed to dissolve, concentrate to smaller volume after filtration). The analytical sample is dried overnight in vacuo at 35°C. The yellow solid (m.p. 218-221°C, dec) is a mixture of Z and E isomers in approximately 6:1 ratio (NMR). NMR (DMSO-d₆, 400 MHz): δ 1.84 (s, 2-CH₃, minor E isomer), 2.12 (s, 2-CH₃, major Z isomer), 3.55 (s, 2H, CH₂COO), 5.41 (s, ArCH₂O, possibly E isomer), 5.44 (s, ArCH₂O, possibly Z isomer), 6.70 (dt, 1H, ArH), 6.85-7.3 (m, 1H, ArH), 7.18 (d, 2H, J 8.7 Hz, ArH), 7.28 (s, 1H, ArH), 7.32-7.40 (m, 1H, ArH), 7.51 (d, 2H, J 8.6 Hz, ArH), 7.62 (t, 1H, J ca. 7 Hz, ArH), 7.68-7.76 (m, 1H, ArH), 7.79 (t, J, 7 Hz, 1H, ArH), 8.01 (nm, 2H, ArH), 8.44 (d, 1H, 8.5 Hz, ArH), 12.4 (broad s, 1H, COOH). MS (CI, m/z): 452 (M+H)⁺, 408 (M-COOH)⁺.

25 Analysis for: C₂₉H₂₂FNO₃

Calculated: C, 77.15; H, 4.91; N, 3.10.

Found: C, 77.08; H, 4.93; N, 3.12.

Example 5

30 2-Methyl-3-[[4-(methylthio)phenyl]methylene]-6-[(2-naphthyl)methoxyl]-3H-indene-1-acetic acid

A. 6-[(2-Naphthyl)methoxyl]-2-methyl-indanone

A mixture of the indanone (14 g, 86.4 mmole) prepared as described in Example 1, Step D, anhydrous K₂CO₃ (11.24 g, 81.4 mmole), 18-crown-6 (2.29 g, 6.4 mmole) and 2-bromomethylnaphthalene (11.6 g, 95 mmole) in acetonitrile

- 28 -

(275 mL) is heated under nitrogen for 24 hours (in an oil bath set at 70°C). The acetonitrile is evaporated and the residue is dissolved in water, extracted with ethyl acetate, dried (MgSO₄) and evaporated to dryness. The crude product (tan solid) is flash chromatographed (on silica Merck-60, preabsorbed in CH₂Cl₂, eluted with 8:2
5 hexane-ethyl acetate) to provide the title compound as a white solid (13.49 g, 52%).

NMR (CDCl₃, 400 MHz): δ 1.30 (d, J 3.2 Hz, 3H, 2-CH₃), 2.70 (m, 2H, ArCH₂C),
3.35 (m, 1H, CHCO), 5.25 (s, 2H, ArCH₂O), 7.32 (m, 3H, ArH), 7.50 (m,
3H, ArH), 7.85 (m, 4H, ArH).

MS (EI, m/z): 302 (M)⁺, 141.

10 B. I) 6-[(2-Naphthyl)methoxy]-2-methyl-indan-1-ylidene-acetic acid ethylester
(Z isomer)

II) 6-[(2-Naphthyl)methoxy]-2-methyl-indan-1-ylidene-acetic acid ethylester
(E isomer)

15 III) 5-[(2-Naphthyl)methoxy]-2-methyl-indene-3-acetic acid ethyl ester

Triethylphosphonoacetate (19.8 g, 88.3 mmole) is added dropwise
under nitrogen to a stirred and cooled suspension of NaH (60% in oil, 3.53 g,
88.2 mmole) in toluene (225 mL). The cooling bath is removed. A clear solution is
obtained after 10 minutes at room temperature. A solution of the indanone (13.3 g,
44 mmole) of Step A, in toluene (40 mL) is added dropwise and the mixture is placed
20 in an oil bath heated at 100°C for 54 hours (follow by TLC, hexane-ethyl acetate 7:3).
Water is added, the layers are separated and the aqueous phase is reextracted with ethyl
acetate (3 times). The extracts are dried (K₂CO₃) and evaporated to dryness to yield the
crude product as an amber oil (21.5 g), mixture of endo and exo isomers. Flash
chromatography of this crude material (on silica Merck-60, preabsorbed in CH₂Cl₂,
25 hexane-ethyl acetate 9:1) provides small amounts of each of the pure isomers (i.e. I, II
and III) together with mixed fractions and unreacted starting material (ca. 5.24 g). The
structures of the isomers are confirmed by MS and NMR and assigned by NOE. The
mixture of endo and exo esters is routinely used in the next step (combined yield
8.94 g or 54.7%; 90% based upon recovered starting material).

30 Isomer I

NMR (CDCl₃, 400 MHz): δ 1.26 (d, J 6.8 Hz, 3H, 2-CH₃), 1.32 (t, J 7 Hz, 3H,
ester CH₃), 2.54 (d, J 15.1 Hz, 1H, ArCHC), 3.1 (m, 2H, ArCHC + CCH),
4.22 (q, J 7.2 Hz, 2H, ester CH₂), 5.28 (s, 2H, ArCH₂O), 5.85 (s, 1H,
C=CH-COO), 7.04 (dd, 1H, J 8.4 Hz and 2.5 Hz, ArH), 7.17 (d, J 8.4 Hz,

- 29 -

1H, ArH), 7.49 (m, 2H, ArH), 7.59 (d, J 8.4 Hz, 1H, ArH), 7.82 (m, 3H, ArH), 7.95 (s, 1H, ArH), 8.61 (s, 1H, ArH).

MS (EI, m/z): 372 (M)⁺, 231, 141 (b.p.).

Isomer II

5 NMR (CDCl₃, 400 MHz): δ 1.21 (d, 3H, J 7 Hz, 2-CH₃), 1.33 (t, 3H, J 7.1 Hz, ester CH₃), 2.56 (d, J 16.3 Hz, 1H, ArCHC), 3.18 (dd, J 16.3 and 7.1 Hz, 1H, ArCHC), 3.88 (m, 1H, CCH), 4.22 (q, J ca. 7 Hz, 2H, ester CH₂), 5.24 (s, 2H, ArCH₂O), 6.19 (s, 1H, C=C-COOEt), 7.06 (dd, J 8.4 and 2.4 Hz, 1H, ArH), 7.17 (d, J 2.3 Hz, 1H, ArH), 7.23 (d, J 8.4 Hz, 1H, ArH), 7.49 (m, 2H, ArH), 7.54 (dd, J 8.4 and 1.6 Hz, 1H, ArH), 7.88 (m, 4H, ArH).

10 MS (CI, m/z): 373 (M+H)⁺, 261 (b.p.), 233

Isomer III

15 NMR (CDCl₃, 400 MHz): δ 1.20 (t, J 7 Hz, 3H, ester CH₃), 2.11 (s, 3H, 2-CH₃), 3.28 (s, 2H, ArCH₂), 3.48 (s, 2H, CH₂COO), 4.09 (q, J 7.1 Hz, 2H ester CH₂), 5.25 (s, 2H, ArCH₂O), 6.79 (dd, J 8.1 and 2.3 Hz, 1H, ArH), 6.98 (s, 1H, ArH), 7.24 (d, 8.8 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 7.56 (dd, J 8.4 and 1.7 Hz, 1H, ArH), 7.87 (m, 4H, ArH).

MS (CI, m/z): 373 (M+H)⁺, 285

20 C. 2-Methyl-3-[[4-(methylthio)phenyl]methylene]-6-[(2-naphthyl)methoxy]-3H-indene-1-acetic acid

To a mixture of the ester (mixture of isomers prepared as described above (2.5 g, 6.71 mmole) and 4-(methylthio)-benzaldehyde (1.124 g, 7.38 mmole) in anhydrous methanol (60 mL) is added dropwise under nitrogen 25% methanolic sodium methoxide (2.9 mL). The mixture is refluxed for 16 hours, the solvent removed and the residue slurried in water and stirred overnight (the initial yellow oil turns into a solid). The water is evaporated in vacuo and the residue is triturated with ether (to remove unreacted aldehyde), filtered, washed with ether and dried (yellow solid, 2.65 g). The crude sodium salt is slurried in water and acidified (to pH 6.5) with 10% acetic acid. The acid is collected, washed and dried in vacuo. It is again washed with ether and dried (1.02 g, 32%, m.p. 209-211°C, dec.). The NMR shows it to be a mixture of Z and E isomers in approximately 8:1 ratio.

30 NMR (DMSO-d₆, 400 MHz): δ 1.81 (s, 2-CH₃, minor isomer E), 2.11 (s, 2-CH₃, major isomer Z), 2.51 (s, 3H, SCH₃), 3.54 (s, 2H, CH₂COO), 5.23 (s, ArCH₂O, Z isomer) and 5.28 (s, ArCH₂O, E isomer), 6.60 (dd, 1H, ArH),

- 30 -

6.90 (d, J 2.2 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.27-7.36 (m, 3H, ArH), 7.46-7.62 (m, 5H, ArH), 7.88-8.00 (m, 4H, ArH), 12.33 (broad s, 1H, COOH).

MS (CI, m/z): 479 (M+H)⁺, 435 (M+H-COO)⁺, 141 (C₁₁H₉, naphthyl)⁺.

- 5 Analysis for: C₃₁H₂₆O₃S
 Calculated: C, 77.80; H, 5.48.
 Found: C, 77.44; H, 5.47.

Example 6

10 3-[(4-Chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid

A. 5-Hydroxy-2-methyl indene-3-acetic acid

A mixture of the indanone (1.81 g, 11.17 mmole) of Example 1, Step D, cyanoacetic acid (1.05 g, 12.3 mmol) ammonium acetate (0.17 g), acetic acid (0.66 g) and toluene (5 mL) is heated at reflux with water removal (Dean-Stark) for 24
15 hours (TLC, CH₂Cl₂-ethyl acetate 8:2). The toluene is evaporated and the residual yellow solid is redissolved in ethanol (6 mL) containing 2.2 N-KOH (1.4 mL). A solution of KOH (2.2 g, 85) in water (15 mL) is added and the solution is refluxed under nitrogen for 18 hours. The ethanol is evaporated, the residue is diluted with water and extracted with ether (2 times). The aqueous layer is acidified in the cold with
20 6N-HCl (to pH 3) and extracted with ethyl acetate. The extracts are washed with brine, dried (MgSO₄) and evaporated to provide the crude title compound together with traces of unreacted indanone. It is used as such in the next step.

NMR (DMSO-d₆, 200 MHz): δ 2.02 (s, 3H, 2-CH₃), 3.2 (s, 2H, ArCH₂), 3.4 (s, 2H, CH₂COO), 6.48 (d, 1H, ArH), 6.6 (s, 1H, ArH), 7.1 (d, 1H, ArH), 9.08
25 (broad, 1H, OH).

B. 5-Hydroxy-2-methyl-indene-3-acetic acid methylester

To a solution of the crude acid as prepared in Step A, above, in dry methanol (120 mL) is added p-toluenesulfonic acid monohydrate (1.9 g) and the mixture is gently refluxed for 1.5 hours. The methanol is evaporated, the residue
30 dissolved in ethyl acetate, washed with brine and dried (MgSO₄). Removal of the solvent provides a brown oil that readily solidifies upon drying in vacuo. The residue is flash chromatographed (silica Merck-60, absorbed in dichloromethane, eluted with dichloromethane-ethylacetate 98:2 and 94:6) to yield the pure title compound as an off-white solid (9.4 g, 80%).

- 31 -

NMR (CDCl₃, 400 MHz): δ 2.1 (s, 3H, 2-CH₃), 3.26 (s, 2H, ArCH₂), 3.49 (s, 2H, CH₂COO), 3.67 (s, 3H, COOCH₃), 4.89 (broad s, OH), 6.59 (dd, 1H, ArH), 6.75 (d, 1H, J 2.4 Hz, ArH), 7.18 (d, 1H, 7.9 Hz, ArH).

MS (EI, m/z): 218 (M)⁺, 158 (b.p.).

5 C. 3-[(4-Chlorophenyl)methylene]-[2-methyl-6-hydroxy]-3H-indene-1-acetic acid

To a solution of sodium metal (0.170 g, 7.39 g.a.) in anhydrous methanol (2.5 mL) under nitrogen is added dropwise with cooling a solution of the ester (0.537 g, 2.46 mmole) of step B, in methanol (5 mL) followed by p-chlorobenzaldehyde (0.381 g, 2.71 mmole, 1.1 equiv.). The mixture is stirred in an oil bath
10 heated at 65-70°C for 6 hours followed by standing overnight at room temperature (TLC, CH₂Cl₂-ethyl acetate 93:7). Water (10 mL) and methanol (2 mL) are added and the mixture is again refluxed under nitrogen for 3 hours (TLC, CH₂Cl₂-ethyl acetate 90:10). The methanol is evaporated, the residue is dissolved in water, and washed with ether (2 times). The aqueous phase is acidified in the cold with 6N-HCl
15 (to pH 3) and extracted with ethyl acetate. The extracts are washed (brine) and evaporated to yield a greenish-yellowish solid (0.8 g). The NMR spectrum shows that it is a mixture of the title compound and 5-hydroxy-2-methyl-indene-3-acetic acid. They are best separated as their methylesters (see below).

20 D. 3-[(4-Chlorophenyl)methylene]-[2-methyl-6-hydroxy]-3H-indene-1-acetic acid methylester

A solution of the crude acids (2.46 mmole, obtained as described in Step C, above) in methanol (10 mL) containing p-toluenesulfonic acid monohydrate (60 mg) is refluxed for 5 hours. The methanol is evaporated and the residue dissolved in ethyl acetate, washed with brine and dried (MgSO₄). The solvent is evaporated and
25 the residue is flash chromatographed (on silica Merck-60, absorbed in 1:1 dichloromethane-hexane, eluted with toluene-isopropanol 95:5) to provide the title compound (less polar spot, 0.103 g, yellow solid) together with some impure material (0.390 g, oil that solidifies upon standing). The Z configuration is confirmed by NOE. The more polar spot is identical (NMR, TLC) with methyl-5-hydroxy-2-methylindene-3-acetate.
30

NMR (CDCl₃, 400 MHz): δ 2.17 (s, 3H, 2-CH₃), 3.55 (s, 2H, CH₂COO), 3.69 (s, 3H, COOCH₃), 6.33 (dd, 1H, ArH), 6.67 (d, J 2.3 Hz, 1H, ArH), 7.01 (s, 1H), 7.14 (d, J 8.3 Hz, 1H, ArH), 7.40 (dd, 4H, ArH).

MS (EI, m/z): 342/340 (1 Cl, M)⁺, 231 (b.p.)

- 32 -

E. 3-[(4-Chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid methylester

A mixture of the ester (0.410 g, 1.2 mmole) of Step D, anhydrous potassium carbonate (0.17 g), and 18-crown-6 (0.050 g) in acetonitrile (7 mL) is stirred at room temperature for 15 minutes. 2-Chloromethylquinoline is added (free base, 0.149 g, 1.42 mmole, freshly prepared from the hydrochloride salt) and the deep red mixture is stirred under nitrogen for 15 hours in an oil bath heated at 65°C. A 10% excess of potassium carbonate, crown ether and the 2-chloromethylquinoline is then added and the reflux is continued for another 2 hours (TLC, hexane-isopropanol 93:7). The solvent is evaporated and the residue is partitioned between water and ethyl acetate. The organic phase is washed (brine), dried (MgSO₄) and evaporated to dryness. The crude product is identical (NMR, TLC) with the material described in Example 7, below.

F. 3-[(4-Chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid

1N-KOH (3.72 mL) is added dropwise to a warm solution of the ester (0.600 g, 1.24 mmole) of Step E, in methanol (7 mL). The mixture is refluxed under nitrogen for 3 hours. After stirring overnight at room temperature (TLC, hexane-isopropanol 93:7), the methanol is evaporated and the residue washed with ether. The solid is slurried in water, neutralized in the cold with 10% acetic acid (to pH 6-6.5) and extracted with ethyl acetate (vigorous stirring is necessary to achieve solution). The extracts are washed with brine, dried (MgSO₄) and evaporated to yield the crude acid (0.250 g, 43%). It is recrystallized from hot ethyl acetate/methylene chloride (dissolve in a large volume and concentrate the filtrate until precipitation occurs). The pure title compound (m.p. 216-218°C) is identical (TLC, NMR) with the material described in Example 1, Step G. (Z isomer).

Example 7

3-[(4-Chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid methylester

30 A suspension of the acid (1.88 mmole, crude material before purification, obtained as described in Example 1, Step G), in methanolic HCl (15 mL) is refluxed until the reaction is complete by TLC (dichloromethane-methanol 9:1, UV). The methanol is evaporated and the residue is partitioned between ethyl acetate and

- 33 -

dilute NH_4OH . The extracts are washed with brine, dried (K_2CO_3) and evaporated to dryness to provide a yellow oil that foams in vacuo (0.900 g). The crude product is flash chromatographed (on silica Merck-60, toluene-hexane-isopropanol 50:50:1 as eluent) to yield the pure title compound (0.630 g, yellow foam that solidifies upon trituration with ethanol, 69.6% over 2 steps). Mixture of Z and E isomers in approximately 4:1 ratio (based upon the position of the 2- CH_3 signal in the NMR spectrum). NMR (CDCl_3 , 400 MHz): δ 1.81 (s, 2- CH_3 , minor isomer E), 2.17 (s, 2- CH_3 , major isomer Z), 3.56 (s, 2H, CH_2COO), 3.62 (s, 3H, OCH_3) 5.42 (s, 2H, ArOCH_2), 6.52 (dd, 1H, ArH), 6.89 (d, J 2.4 Hz, 1H), 7-8.3 (m, 12H, ArH). MS (+FAB, m/z): 482 (1Cl, $\text{M}+\text{H}$)⁺, 360, 217, 143 (b.p.)⁺, 91.

Example 8

1,8-Diethyl-1,3,4,9-tetrahydro-6-(2-quinolinyl-methoxy)pyrano[3,4-b]indole-1-acetic acid

A. 7-Ethyl-2,3-dihydrotryptophol

A mixture consisting of 7-ethyltryptophol (28.0 g, 0.148 mol) and 250 mL of trifluoroacetic acid is stirred at room temperature. Sodium borohydride pellets (5.4 g, 0.145 mol) are added over a 4 hour period. After addition is complete, the reaction is stirred for 1 hour. The reaction mixture is poured onto ice and neutralized with 50% NaOH to pH 10. The aqueous layer is extracted with ether (3 x 200 mL). The ether layers are combined and extracted with 5% HCl solution (3 x 200 mL). The combined acidic solution is then made alkaline with 50% NaOH and extracted with ether (3 x 200 mL). The combined ether layers are washed with water (2 x 200 mL), once with brine (200 mL), dried (MgSO_4), filtered and concentrated to afford 17.3 g of oil. Flash chromatography using 60% ethyl acetate/hexane, and then 80% ethyl acetate/ hexane affords 13.5 g of solid title compound, m.p. 73-75°C.

NMR (CDCl_3): δ 6.98 (d, J=8.3 Hz, 1H, Ar), 6.93 (d, J=5.3 Hz, 1H, Ar), 6.74 (t, J=7.5 Hz, 1H, Ar), 3.7 (m, 3H, OCH_2OH), 3.68 (m, 2H, NH-CH_2), 3.56 (m, 1H), 3.33 (m, 1H, NH-CH_2), 2.49 (q, J=7.6 Hz, 2H, CH_2CH_3), 2.11 (m, 1H, CH_2CH_2), 1.80 (m, 1H, CH_2CH_2), 1.21 (t, J=7.6 Hz, CH_2CH_3).

MS: m/e 191 (M^+), 130, 118.

B. 7-Ethyl-5-hydroxytryptophol

A solution of potassium nitrosodisulfonate (17.0 g, 0.063 mol) in pH 7 buffer (760 mL) is added over a 20 minute period to a stirring solution of 7-

- 34 -

ethyl-2,3-dihydrotryptophol (5.0 g, 0.026 mol) in 350 mL of acetone. Ten minutes after the addition is complete, the reaction mixture is extracted with ethyl acetate (4 x 300 mL). The combined ethyl acetate layers are washed with distilled water (2 x 200 mL), once with brine (200 mL), dried (MgSO₄) and concentrated to afford 5.6 g of crude product. The crude product is loaded onto a flash chromatography column. The next day, it is flashed using 70% ethyl acetate/hexane to afford 2.5 g of title compound.

NMR (DMSO-d₆): δ 8.43 (s, 1H, 6.97 (d, J=2.3 Hz, 2H, arom), 6.60 (d, J=2.1 Hz, 1H, arom), 6.40 (d, J=2.1 Hz, 1H, arom), 4.55 (t, J=5.3 Hz, 1H, CH₂OH), 3.57 (m, 2H), 3.32 (s, 1H, Ar-OH), 2.7 (m, 4H), 1.20 (t, J=7.5 Hz, 3H).

MS: 205 (M)⁺, 174, 159.

Analysis for: C₁₂H₁₅NO₂

Calculated: C, 70.22; H, 7.37; N, 6.82.

Found: C, 70.15; H, 7.52; N, 6.60.

15 C. 1,8-Diethyl-1,3,4,9-tetrahydro-6-hydroxypyranol[3,4-b]indole-1-acetic acid methyl ester

A mixture consisting of 7-ethyl-5-hydroxytryptophol (15.5 g, 0.076 mol), 20% tetrahydrofuran/methylene chloride (1200 mL), methyl 3-methoxy-2-pentenoate (17.5 g, 0.0121 mol) and boron trifluoride etherate (23.0 mL, 0.187 mol) is stirred at room temperature for 28 hours. The reaction mixture is diluted with 100 mL of methylene chloride and washed with 5% NaHCO₃ (3 x 500 mL), once with water, dried (MgSO₄) and concentrated to give 30.3 g of crude. Flash chromatography using 25% ethyl acetate/hexane as an eluent afforded 16.0 g of title compound, m.p. 153-154°C.

25 NMR (CDCl₃): δ 8.90 (bs, 1H), 6.74 (d, J=23 Hz, H, arom), 6.49 (d, J=2.4 Hz, 1H, arom), 4.50 (s, 1H, Ar-OH), 4.00 (m, 2H), 3.7 (s, 3H), 3.0-2.70 (m, 6H), 2.20 (m, 2H), 1.33 (t, J=7.6 Hz, 3H), 0.82 (t, J=7.6 Hz, 3H).

MS: 317 (M)⁺, 288, 244.

Analysis for: C₁₈H₂₃NO₄

30 Calculated: C, 68.12; H, 7.30; N, 4.41.

Found: C, 67.73; H, 7.23; N, 4.24.

D. 1,8-Diethyl-1,3,4,9-tetrahydro-6-hydroxypyranol[3,4-b]indole-1-acetic acid

A mixture consisting of the methyl ester (43.1 g, 0.136 mol) of Step C, potassium hydroxide (2.4 g, 0.407 mol), 1600 mL of methanol and 160 mL water is refluxed for 5 hours under a nitrogen atmosphere. The excess methanol is

- 35 -

evaporated and water (1000 mL) is added to the residue. The mixture is extracted with ether (3 x 500 mL). The aqueous layer is made acidic with 5% HCl (pH 2), then extracted with chloroform (4 x 300 mL). The combined chloroform layers are washed with water (2 x 500 mL), brine (500 mL), dried (MgSO₄), and concentrated under vacuo to yield 43.0 g of foam. Flash chromatography using 15% acetone/toluene as eluent, affords 40.0 g of foam. This is crystallized from acetonitrile/toluene to afford 35.4 g of pure title compound, m.p. 172-173°C.

¹H NMR (DMSO-d₆): δ 8.44 (s, 1H, -NH), 6.51 (d, J=2.1 Hz, 1H, Ar), 6.39 (d, J=1.96 Hz, 1H, Ar), 3.89 (m, 2H), 2.89 (q, 2H), 2.87 (d, J=13.5 Hz, 1H, CH₂COOH), 2.75 (d, J=15.8 Hz, 1H, CH₂COOH), 2.71-2.57 (m, 2H), 1.99 (q, J=7.2 Hz, 2H), 1.20 (t, J=7.6 Hz, 3H), 0.60 (t, J=8.5 Hz, 3H).

IR (KBr, cm⁻¹): 3590 (OH), 1720 (CO).

UV (MeOH, nm): 276 (9940), 295 (6400).

MS: m/e 303 (M⁺), 244.

15 Analysis for: C₁₇H₂₁NO₄

Calculated: C, 67.31; H, 6.98; N, 4.62.

Found: C, 66.99; H, 6.80; N, 4.96.

E. 1,8-Diethyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid

20 A mixture consisting of 1,8-diethyl-1,3,4,9-tetrahydro-6-hydroxy-pyrano[3,4-b]indole acetic acid methyl ester (5.0 g, 0.0158 mol), dimethylsulfoxide (250 mL), and potassium iodide (150 mg) is stirred at room temperature. A solution of sodium hydroxide (3.9 g, in 20 mL H₂O) is added and stirred at room temperature followed by addition of 2-chloromethyl quinoline hydrochloride (8.4 g, 0.0392 mol).
25 The reaction mixture is heated at 70-80°C for 3.5 hours, cooled and diluted with water (100 mL). The mixture is made acidic with 1N HCl to pH 4, and extracted with ethyl acetate (3 x 400 mL). The combined organic layers are washed with water (3 x 200 mL), once with brine (200 mL), dried over MgSO₄, filtered and concentrated to give 10.0 g of crude product. The crude product is chromatographed on silica
30 gel using 7% methanol/methylene chloride as eluent to afford 2.9 g pure product. The latter is dissolved in 200 cc ethyl acetate and precipitated by dropwise addition to petroleum ether (700 mL) to afford 2.7 g of the title compound, m.p. 179-181°C.

¹H NMR (400 MHz, DMSO-d₆): δ 8.38 (d, J=8.5 1H, 4Q), 8.0 (d, J=8.6 1H, 8-Q), 7.97 (d, J=7.2, 1H-5Q), 7.76 (dt, J₁=6.8, J₂=1.5 1H, 7Q), 7.70 (d, J=8.5 1H 3Q), 7.58 (dt, J₁=6.9, J₂=1.1 1H 6Q), 6.86 (d, J=2.2 1H ar.), 6.67 (d, J=2.2

- 36 -

1H ar.), 5.32 (s, 2H-OCH₂Q), 3.6 (m, 2H), 2.79 (m, 2H), 2.74 (d, J=15.2 1H), 2.64 (d, J=14.2, 1H), 2.55 (m, 2H), 2.0 (q, J=7.2, 2H, CH₂CH₃), 1.22 (5, J=7.5 3H CH₂CH₃), 0.66 (t, J=7.2 3H, 8 CH₂CH₃).

IR: (KBr): 3400 (NH, OH), 1740 (C=O) cm⁻¹.

5 Mass: (M+H), 445, 239, 217.

Analysis for: C₂₇H₂₈N₂O₄

Calculated: C, 72.95; H, 6.35; N, 6.30.

Found: C, 71.04; H, 6.19; N, 6.21.

Example 9

10 1-Ethyl-1,3,4,9-tetrahydro-6-(quinolinylmethoxy)- pyrano[3,4-b]indole-1-acetic acid

A. 1-Ethyl-1,3,4,9-tetrahydro-6-(phenylmethoxy)pyrano[3,4-b]indole-1-acetic acid methyl ester

A mixture consisting of 5-benzyloxytryptophol (24.0 g, 0.090 mol),
15 methylene chloride (600 mL), methyl 3-methoxy-2-pentenoate (16.8 g, 0.177 mol)
and borontrifluoride etherate (2 mL) is stirred at room temperature for 3 hours. The
reaction mixture is washed with 5% NaHCO₃ (2 x 200 mL), water (2 x 200 mL)
and once with brine (200 mL), dried (MgSO₄), filtered and concentrated to give
38.0 g crude product. The crude product is flash chromatographed on silica gel using
20 20% ethyl acetate/hexane as an eluent to afford 29.0 g pure title compound, m.p. 98-
100°C.

¹H NMR, CDCl₃): δ 8.87 (BS, 1H NH), 7.47 (d, J=7.3, 2H Bz), 7.36 (t, J=7.6, 2H
Bz), 7.29 (m, 1H), 7.24 (d, J=7.5, 1H), 7.04 (d, J=2.4, 1H), 6.91 (dd,
J₁=8.7, J₂=2.4, 1H), 5.10 (s, 2H O-CH₂-Bz) 4.06-3.90 (m, 2H), 3.71 (s, 3H
25 CH₂COOCH₃), 2.99 (d, J=16.6, 1H), 2.89 (d, J=16.6 1H), 2.75 (m, 2H),
2.0 (m, 2H), 0.81 (t, J=7.4 3H CH₂CH₃).

Mass: (M⁺) 379, 350, 288.

Analysis for: C₂₃H₂₅NO₄

Calculated: C, 72.80; H, 6.64; N, 3.69.

30 Found: C, 72.61; H, 6.63; N, 3.69.

B. 1-Ethyl-1,3,4,9-tetrahydro-6-(phenylmethoxy)pyrano[3,4-b]indole-1-acetic acid

A mixture consisting of the ester (29.0 g, 0.0765 mol) of Step A,
methanol (800 mL), water (50 mL) and potassium hydroxide (16.0 g, 0.29 mol) is

- 37 -

refluxed for 4 hours. The reaction mixture is cooled to room temperature, concentrated and diluted with water (500 mL). The aqueous layer is washed with ether (2 x 200 mL) and made acidic with a 1:1 mixture of concentrated HCl and water to pH 2.71 is extracted with chloroform (4 x 300 mL) and the combined chloroform layers are washed once with water (2 x 300 mL), once with brine (300 mL), dried (MgSO₄), filtered and concentrated to give 26.0 g of title compound, m.p. 163-165°C. ¹H NMR (400 MHz; CDCl₃): δ 8.39 (BS, NH), 7.47 (d, J=7.4, 2H), 7.38 (dt, J₁=7.1, J₂=1.8, 2H), 7.30 (m, 1H), 7.22 (d, J=8.7, 1H), 7.04 (d, J=2.4 1H), 6.90 (dd, J₁=8.8, J₂=2.4 1H), 5.10 (s-OCH₂ Bz) 4.08 (m, 2H), 3.02 (d, J=16.4 1H), 2.95 (d, J=16.3, 1H), 2.80 (q, J=5.0 2H), 2.06 (m, 2H), 0.86 (t, J=7.3 3H CH₂CH₃).

IR (KBr): 3380 (NH), 1710 (CO) cm⁻¹.

Mass: (M⁺) 365, ions 336, 306.

Analysis for: C₂₂H₂₃NO₄

15 Calculated: C, 72.31; H, 6.34; N, 3.83.

Found: C, 72.17; H, 6.29; N, 3.65.

C. 1-Ethyl-1,3,4,9-tetrahydro-6-hydroxy-pyrano[3,4-b]indole-1-acetic acid

A mixture consisting of 10% Pd/c on charcoal (3.5 g), ethanol (800 mL), tetrahydrofuran (100 mL) and the acid (21.0 g, 0.056 mol) of Step B, is hydrogenated at 30 psi for 18 hours. The reaction mixture is filtered and concentrated to give 21.0 g of crude product, which is used in the next reaction without further purification.

25 ¹H NMR (DMSO-d₆): δ 10.36 (s, NH), 7.16 (d, J=7.4, 1H Ar), 6.68 (d, J=2.2 1H Ar), 6.53 (dd, J₁=8.5, J₂=2.2 1H Ar), 3.89 (m, 2H), 2.82 (d, J=13.6, 1H), 2.62 (d, J=13.6, 1H), 2.58 (m, 2H), 2.0-1.90 (m, 2H), 0.61 (t, J=7.3 3H CH₂CH₃).

IR (KBr): Broad peak. 3700-3300 cm⁻¹ (NH, OH), 1710 cm⁻¹ (C=O).

Mass: M ion: 275, ion 246, 216, 202.

Analysis for: C₁₅H₁₇NO₄

30 Calculated: C, 65.44; H, 6.22; N, 5.09.

Found: C, 68.82; H, 6.72; N, 4.81.

D. 1-Ethyl-1,3,4,9-tetrahydro-6-(quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid

35 A mixture consisting of the 6-hydroxy pyrano acid (21.0 g, 0.076 mol) of Step C, dimethyl sulfoxide (900 mL), sodium hydroxide (180.0 g in 100 mL

- 38 -

H₂O) and 2-chloromethylquinoline hydrochloride (23.0 g, 0.0107 mol) is heated to 70-80°C for 1 hour. The reaction mixture is cooled, poured into water (1500 mL) and made acidic with 1N HCl to pH 4. It is extracted with ethyl acetate (4 x 500 mL) and the combined organic layers are washed once with water (2 x 300 mL), once with
 5 brine (300 mL), dried (MgSO₄), filtered and concentrated to give 33.0 crude product, which is chromatographed on silica gel using 7% methanol/methylene chloride as eluent to afford 13.9 g pure product. The pure product is dissolved in 100 mL ethyl acetate, and precipitated by adding dropwise to petroleum ether (3000 mL), and filtered to give 13.8 g product, which is crystallized from benzene to give 12.0 g of pure product,
 10 m.p. 105°C (dec.).

¹H NMR DMSO-d₆: δ 10.59 (s, 1H, NH), 8.39 (d, J=8.5, 1H, 4Q), 8.01 (d, J=8.5, 1H, 8Q), 7.97 (d, J=8.2, 1H, 5Q), 7.78 (dt, J₁=6.9, J₂=1.4, 1H 7Q), 7.70 (d, J=8.5, 1H, 3Q), 7.60 (dt, J₁=6.9, J₂=1.0, 1H, 6Q), 7.21 (d, J=8.7, 1H ar.), 7.06 (d, J=22.3, 1H Ar), 6.82 (dd, J₁=8.7, J₂=2.5, 1H Ar.), 5.34 (s, 2H, O-CH₂-Q), 3.92-3.86 (m, 2H), 2.82 (d, J=13.6, 1H), 2.62 (d, J=18.6, 1H),
 15 2.60 (m, 2H), 2.01-1.91 (m, 2H), 0.61 (t, J=7.3, CH₂CH₃).

IR (KBr): 3400 cm⁻¹ (NH,OH) 1705 cm⁻¹ (C=O).

Mass: FAB: M+H 417 ion M⁺ 357.

Analysis for: C₂₅H₂₅N₂O₄

20 Calculated: C, 72.10; H, 5.81; N, 6.73.

Found: C, 72.55; H, 5.91, N, 6.48.

Example 10

1-Methyl-1,3,4,9-tetrahydro-6-(2-quinolinyl-methoxy)pyrano[3,4-b]indole-1-acetic acid

25 A. 1-Methyl-1,3,4,9-tetrahydro-6-(phenylmethoxy)pyrano[3,4-b]indole-1-acetic acid, ethyl ester

A mixture consisting of 5-benzyloxytryptophol (4.5 g, 0.017 mol), benzene (200 mL), ethyl acetoacetate (3.4 g, 0.026 mol) and p-toluenesulfonic acid (0.5 g) is refluxed for 2.5 hours using a Dean-stock trap to remove the water. The
 30 reaction mixture is cooled to room temperature and washed with 5% sodium bicarbonate, (1 x 200 mL), water (200 mL) and brine (100 mL), dried (MgSO₄), filtered and concentrated to give 8.0 g of crude product as a thick oil, which is flash chromatographed on silica gel using 20% ethyl acetate/hexane as an eluent to afford 5.5 g oil which solidifies upon standing, m.p. 96-98°C.

- 39 -

¹H NMR 400 MHz CDCl₃: δ 8.96 (bs, 1H, NH), 7.47 (d, J=7.0, 2H ar., O-Bz), 7.36 (dt, J₁=7.1, J₂=1.8, 2H Ar., O-CH₂Bz), 7.3 (m, 1H, OCH₂-Bz), 7.23 (d, J=8.7 1H Ar.), 7.04 (d, J=2.5, 1H Ar.), 6.90 (dd, J₁=8.7, J₂=2.3 1H Ar), 5.10 (s, 2H, O-CH₂-Ø), 4.22-4.14 (m, 2H), 4.01 (m, 2H), 2.98 (d, J=16.5, 1H), 2.85 (d, J=16.4, 1H), 2.79 (t, J= 2H), 1.7 (s, 3H, CH₂), 1.3 (t, J= 3H COOCH₂CH₃).

Mass: EI: M/e: 379, ions 292, 158.

B. 1-Methyl-1,3,4,9-tetrahydro-6-(phenylmethoxy)pyranof[3,4-b]indole-1-acetic acid

10 A mixture consisting of the ester (5.5 g, 0.013 mol) of Step A., methanol (300 mL), water (20 mL) and potassium hydroxide (4.0 g, 0.071 mol) is refluxed for 4 hours. The reaction mixture is cooled to room temperature, concentrated, diluted with water (200 mL) and made acidic with a 1:1 solution of concentrated HCl:water to pH of 1. The mixture is extracted with chloroform (3 x 150 mL), the
15 combined chloroform extracts are washed once with water (2 x 100 mL), once with brine (100 mL), dried (MgSO₄), filtered and concentrated to give 4.6 g of product, which is used in the next reaction, m.p. 157-158°C (dec.).

¹H NMR (400 MHz, DMSO-d₆): δ 11.98 (bs, 1H, COOH), 10.62 (s, 1H, NH), 7.45 (d, J=7.1, 2H-Bz), 7.38 (dt, J₁=7.1, J₂=1.8, 2H, Bz), 7.30 (m, 1H, Bz), 7.18 (d, J=8.7, 1H Ar.), 6.99 (d, J=2.3, 1H Ar.), 6.76 (dd, J₁=8.7, J₂=2.5, 1H Ar.), 5.07 (s, 2H, OCH₂Ø), 3.95-3.84 (m, 2H), 2.78 (d, J=13.8, 1H), 2.68 (d, J=13.8, 1H), 2.60 (t, J=5.4, 2H), 1.56 (s, 3H).

Mass: EI: M/e: 351, ions 292, 260, 130.

C. 1-Methyl-1,3,4,9-tetrahydro-6-hydroxy-pyranof[3,4-b]indole-1-acetic acid

25 A mixture consisting of the acid (4.5 g, 0.013 mol) of Step B, ethanol (150 mL), tetrahydrofuran (20 mL) and 10% Pd/c on charcoal (800 mg) is hydrogenated at 30 psi for 18 hours. The mixture is filtered and concentrated to give 3.1 g of product, which is used into next reaction without further purification.

¹H NMR (400 MHz, DMSO-d₆): δ 7.19 (d, J=8.5, 1H Ar.), 6.70 (d, J=2.5, 1H Ar.), 6.55 (dd, J₁=8.5, J₂=2.5, 1H Ar.), 3.90 (m, 2H), 2.77 (d, J₁=16.0, 1H), 2.66 (d, J=16.0, 1H), 2.55 (m, 2H), 1.55 (s, 3H).

Mass: EI: M/e: 261, ions: 216, 160, 101.

- 40 -

D. 1-Methyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid

- A mixture consisting of 1-methyl-1,3,4,9-tetrahydro-6-hydroxy-pyrano[3,4-b]indole-1-acetic acid (3.0 g, 0.011 mol) of Step C, dimethyl sulfoxide (300 mL), potassium iodide (100 mg) and sodium hydroxide (2.5 g in 20 mL water) is stirred at room temperature. 2-Chloromethylquinoline hydrochloride (5.8 g, 0.022 mol) is added and the reaction mixture is heated for 3.5 hours, cooled and diluted with water (700 mL). The mixture is made acidic to pH 4 with 1N HCl, extracted with ethyl acetate (4 x 300 mL) and the combined organic layers are washed once with water (2 x 200 mL), once with brine (200 mL), dried (MgSO₄), filtered and concentrated to yield crude product, which is flash chromatographed on silica gel using 10% methanol/methylene chloride as an eluent to give 1.0 g product. The latter is dissolved in ethyl acetate (20 mL) and precipitated by adding dropwise to petroleum ether (500 mL) to give 1.0 g pure compound, m.p. 175-177°C (dec.).
- ¹H NMR (400 MHz DMSO-d₆): δ 11.2 (bs, 1H, NH), 8.37 (d, J=8.5, 1H 4Q), 8.0 (d, J=8.7 1H, 8Q), 7.97 (d, J=7.6, 1H, 5Q), 7.77 (dt, J₁=6.9, J₂=1.4, 1H, 7Q), 7.69 (d, J=8.5, 1H, 3Q), 7.58 (dt, J₁=7.0, J₂=1.0, 1H, 6Q), 7.18 (d, J=8.7, 1H Ar.), 7.03 (d, J=2.3 1H Ar.), 6.80 (dd, J₁=8.7, J₂=2.3 1H Ar), 5.34 (s, 2H, OCH₂Q), 3.88-3.84 (m, 2H), 2.62 (bs, 2H), 2.48 (bs, 2H), 1.56 (s, 3H-CH₃).
- IR (KBr): 3400 cm⁻¹ (broad NH, OH,), 1700 cm⁻¹ (C=O).
- Mass: EI: M/e: M⁺ 402, ions 202, 157.
- Analysis for: C₂₄H₂₂N₂O₄
- Calculated: C, 71.63; H, 5.57; N, 6.96.
- Found: C, 69.20; H, 5.38; N, 6.60.

Example 11

1-Ethyl-2,3,4,9-tetrahydro-6-(2-quinolinyl-methoxy)-1H-carbazole-1-acetic acid

- A. 1-Ethyl-2,3,4,9-tetrahydro-6-methoxy-1H-carbazole-1-acetic acid methyl ester
- A mixture consisting of 4-methoxyphenylhydrazine (25.0 g, 0.162 mol), 2-carbomethoxymethyl-2-ethylcyclohexanone (42.0 g, 0.212 mol), and toluene (1000 mL) is refluxed for 24 hours under a nitrogen atmosphere and the water is removed using a Dean-Stark trap. The reaction mixture is cooled and concentrated to give crude hydrazone. (≈ 56 g).

- 41 -

The crude hydrazone (56 g) is dissolved in glacial acetic acid (500 mL) and refluxed for 25 minutes. The reaction mixture is cooled to room temperature, poured into water (2000 mL) and extracted with ethyl acetate (4 x 500 mL). The organic layers are combined, washed with 1N NaOH (2 x 500 mL), water (2 x 500 mL), once with brine (500 mL), dried (MgSO₄), filtered and concentrated to give 47.0 g of crude product. The crude product is flash chromatographed using 10% ethyl acetate/hexane as an eluent to afford 18.0 g product; m.p. 72-74°C.

¹H NMR (400 MHz, CDCl₃): δ 8.94 (bs, 1H, NH), 7.19 (d, J=8.0, 1H Ar.), 6.90 (d, J=2.3 1H Ar.), 6.76 (dd, J₁=8.6, J₂=2.3, 1H Ar.), 3.81 (s, 3H, COOCH₃), 3.64 (s, 3H, OCH₃), 2.68-2.62 (m, 4H), 1.95-1.61 (m, 6H), 0.8 (t, J₁=7.6, 3H, CH₂CH₃).

Mass: EI: M/e: 301, ions 272, 228 (base peak).

B. 1-Ethyl-2,3,4,9-tetrahydro-6-hydroxy-1H-carbazole-1-acetic acid

A mixture consisting of the methoxy compound (18.0 g, 0.060 mol) of Step A, and 48% hydrobromic acid (450 mL) is heated at 125°C for 6 hours. The reaction mixture is cooled, diluted with water (1500 mL) and extracted with ethyl acetate (3 x 500 mL). The organic layers are combined and washed once with water (2 x 500 mL), once with brine (500 mL), dried (MgSO₄), filtered and concentrated to give 15.8 g product as a foam.

¹H NMR (400 MHz, DMSO-d₆): δ 10.21 (s, 1H, COOH), 8.45 (bs, 1H, NH), 7.03 (d, J=8.5, 1H Ar.), 6.63 (d, J=1.9, 1H Ar.), 6.48 (dd, J₁=7.3, J₂=1.3, 1H Ar.), 2.54-2.46 (m, 4H), 1.98-1.66 (m, 6H), 0.70 (t, J=7.3, CH₂CH₃).

Mass: EI: M/e: 273 (M⁺) ions 244, 214, 198.

C. 1-Ethyl-2,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)-1H-carbazole-1-acetic acid

A mixture consisting of the hydroxy acid (8.0 g, 0.028 mol) of Step B, dimethyl sulfoxide (500 mL), potassium iodide (100 mg), and sodium hydroxide (7.0 g in 300 mL H₂O 0.175 mol) is stirred at room temperature, for 15 minutes. 2-Chloromethylquinoline hydrochloride (11.8 g, 0.055 mol) is added and the reaction mixture is heated to 70-80°C for 3 hours. The mixture is cooled to room temperature and poured into water (1500 mL), made acidic to pH 4 with 1N HCl, and extracted with ethyl acetate (3 x 500 mL). The organic layers are combined, washed once with water (2 x 300 mL), once with brine (300 mL). The organic layers are combined, washed once with water (2 x 300 mL), once with brine (300 mL), dried (MgSO₄), filtered and concentrated to give 9.0 g of crude product which is flash chromatographed using 10% methanol/methylene chloride as an eluent to give 3.0 g pure

- 42 -

product, which is dissolved in ethyl acetate (20 mL) and added dropwise to petroleum ether (500 mL). The precipitate is filtered off to give 2.5 g product, m.p. 120-125°C.

¹H NMR (400 MHz, DMSO-d₆): δ 10.80 (bs, 1H, NH), 8.37 (d, J=8.5, 1H, 4Q), 8.0 (d, J=8.5, 1H, 8Q), 7.98 (d, J=7.2, 1H 5Q), 7.77 (dt, J₁=6.9, J₂=1.5, 1H, 7Q), 7.69 (d, J=8.5, 1H, 3Q), 7.61 (dt, J₁=6.9, J₂=1.1, 1H, 6Q), 7.14 (d, J=8.7, 1H Ar.), 6.96 (d, J=2.4, 1H Ar.), 6.76 (dd, J₁=8.6, J₂=2.4, 1H Ar.), 5.32 (s, 2H -CH₂Q), 2.52 (bs, 2H), 1.82-1.72 (m, 8H), 0.71 (t, J=7.3, 3H, CH₂CH₃).

IR (KBr): 3410 cm⁻¹ (NH, OH, broad), 1710 cm⁻¹ (C=O).

Mass: M⁺ 415

Analysis for: C₂₆H₂₆N₂O₃

Calculated: C, 75.34; H, 6.32; N, 6.76.

Found: C, 73.49; H, 6.27; N, 6.48.

Example 12

1,3,4,9-Tetrahydro-1-propyl-6-(2-quinolinyl-methoxy)pyrano[3,4-b]indole-1-acetic acid

A. Ethyl-1-propyl-1,3,4,9-tetrahydro-6-(phenylmethoxy)pyrano[3,4-b]indole-1-acetate

A solution of 5-benzyloxytryptophol (4.72 g, 17 mmol) and ethyl butyrylacetate (3.16 g, 20 mmol) in methylene chloride (75 ml) is treated dropwise with boron trifluoride etherate (3 mL) and stirred under nitrogen at room temperature overnight. The reaction mixture is diluted with methylene chloride (250 mL) and sequentially washed with 5% aqueous sodium bicarbonate (2 x 100 mL) and water (2 x 50 mL). The organic phase is dried (MgSO₄), filtered, and evaporated to afford 7.0 g of a crude dark oil. Purification by flash column chromatography (ethyl acetate:hexane, 1:9 eluent) on silica gel (50:1 ratio, 230-400 mesh) affords the title compound (5.5 g, 79%) as a slightly amber oil homogeneous by TLC.

¹H NMR (200 MHz, CDCl₃): δ 8.93 (bs, 1H, NH), 7.25-7.80 (m, 5H, C₆H₅), 7.22 (d, J=9.3 Hz, 1H, 8-ArH), 7.04 (d, J=2.8 Hz, 1H, 5-ArH), 6.91 (dd, J=9.3, 2.8 Hz, 1H, 7-ArH), 5.12 (s, 2H, OCH₂Ar), 3.83-4.40 (m, 4H, CH₂ ester, 3-H's), 3.03, 2.86 (d, J=17.2 Hz, 2H, CH₂CO₂C₂H₅), 2.60-2.87 (m, 2H, 4-H's), 1.82-2.20 (m, 2H, 1-CH₂(α)), 1.25 (t, J=7.0 Hz, 3H, CH₃ ester), 1.00-1.50 (m, 2H, 1-CH₂(β)), 0.86 (t, J=7.0 Hz, 3H, 1-CH₃).

B. Ethyl-1-propyl-1,3,4,9-tetrahydro-6-hydroxypyranol[3,4-b]indole-1-acetate

A suspension of the 6-benzoyloxypyranindole (5.4 g, 13.25 mmol) of Step A, and 10% Pd/C catalyst (600 mg) in ethanol (150 mL) is hydrogenated for 6 hours in a Parr shaker. Filtration of the catalyst and evaporation of the solvent affords the title compound (3.75 g, 89%) as a cream-colored foam homogeneous by TLC.

¹H NMR (200 MHz, CDCl₃): δ 8.90 (bs, 1H, NH), 7.20 (d, J=9.3 Hz, 1H, 8-ArH), 6.92 (d, J=2.8 Hz, 1H, 5-ArH), 6.75 (dd, J=9.3, 2.8 Hz, 1H, 7-ArH), 4.90 (bs, 1H, OH), 3.85-4.40 (m, 4H, CH₂ ester, 3-H's), 3.02, 2.88 (d, J=17.2 Hz, 2H, CH₂CO₂C₂H₅), 2.57-2.88 (m, 2H, 4-H's), 1.82-2.20 (m, 2H, 1-CH₂(α)), 1.25 (t, J=7.0 Hz, 3H, CH₃ ester), 1.00-1.60 (m, 2H, 1-CH₂(β)), 0.87 (t, J=7.0 Hz, 3H, 1-CH₃).

C. 1,3,4,9-Tetrahydro-1-propyl-6-(2-quinolinylmethoxy)pyranol[3,4-b]indole-1-acetic acid

A solution of the 6-hydroxypyranindole (3.5 g, 11 mmol) of Step B, in dimethylsulfoxide (80 mL) is treated with 2.5N NaOH (20 mL, 50 mmol) and stirred at 40°C under nitrogen for 5 minutes. 2-Chloromethylquinoline hydrochloride (4.71 g, 22 mmol) is added as a solid in one aliquot and the reaction mixture heated to 80°C for 30 minutes. After cooling, the pH of the reaction is adjusted to 12.0 with 2.5N NaOH. After extraction with ether (3 x 250 mL), the aqueous layer is carefully acidified to pH 3.0 with 2N HCl and 0.1N HCl (near end point) followed by rapid extraction with ether (4 x 300 mL). The combined ether extracts are washed with water (2 x 200 mL), dried (MgSO₄), and filtered. Evaporation of the solvent affords a crude yellow foam (4.16 g, 88%). Purification by flash column chromatography (methanol:methylene chloride, 5:95 eluent) on silica gel (100:1 ratio, 230-400 mesh) affords an amber foam (2.08 g, 61%) homogeneous by TLC. A concentrated methylene chloride solution of the foam is added dropwise to cooled, rapidly stirred, petroleum ether (200 mL). Filtration of the resulting precipitate yields the title compound as a cream colored amorphous solid (3.2 g, 61%) homogeneous by TLC. After high vacuum drying (36 hours) the compound still retains solvent of crystallization as indicated by NMR, m.p. 100-110°C (dec.).

IR (KBr): 3400 (NH, OH), 1710 (C=O) cm⁻¹.

- 44 -

- ¹H NMR (400 MHz, CDCl₃): δ 8.93 (s, 1H, NH), 8.26 (d, J=8.5 Hz, 1H, 4-Q), 8.19 (d, J=8.6 Hz, 1H, 8-Q), 7.85 (d, J=8.2 Hz, 1H, 5-Q), 7.81 (d, J=8.5 Hz, 1H, 3-Q), 7.76 (dt, J=7.0, 1.2 Hz, 1H, 7-Q), 7.58 (t, J=7.0 Hz, 1H, 6-Q), 7.07 (d, J=2.4 Hz, 1H, 5-ArH), 6.97 (d, J=8.8 Hz, 1H, 8-ArH), 6.84 (d, J=8.8, 2.4 Hz, 1H, 7-ArH), 5.49 (s, 2H, OCH₂Q), 4.03 (ddd, J=11.4, 4.7, 4.3 Hz, 1H, 3-Heq.), 3.92 (ddd, J=11.4, 7.2, 4.8 Hz, 1H, 3-Hax), 3.05 (d, J=16.8 Hz, 1H, 4-Hax), 2.66 (ddd, J=15.4, 4.7, 4.7 Hz, 1H, 4-Heq.), 1.91-2.14 (m, 2H, 1-CH₂(α)), 1.08-1.48 (m, 2H, 1-CH₂(β)), 0.88 (t, J=7.0 Hz, 3H, 1-CH₃).
- 10 MS (EI); m/e 430 (1.4, M⁺), 160 (50, QCH₂OH₂⁺), 143 (100, QCH₃⁺).
- Analysis for: C₂₆H₂₆N₂O₄
- Calculated: C, 72.54; H, 6.09; N, 6.51.
- Found: C, 72.64; H, 7.52; N, 5.41.

Example 13

- 15 **1-Ethyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)-
pyrano[3,4-b]indole-1-acetic acid, methyl ester**

- Trimethylsilyldiazomethane (40 mL, 10% by weight methylene chloride) is added dropwise to a mixture consisting of 1-ethyl-1,3,4,9-tetrahydro-(2-quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid (1.0 g, 0.002 mol) as prepared in Example 9, methylene chloride (150 mL) and methanol (15 mL). The reaction mixture is stirred at room temperature for 1/2 hour, and is concentrated to give 1.2 g of oily residue, which is very difficult to crystallize. The ester is converted to the hydrochloride salt by adding ether/HCl. The hydrochloride salt is recrystallized from methanol/ether to afford 0.75 g pure compound, m.p. 185-187°C.
- 25 ¹H NMR (400 MHz, DMSO-d₆): δ 8.71 (d, J=8.2 Hz, 1H, 4Q), 8.21 (d, J=8.2 Hz, 1H, 8Q), 8.13 (d, J=8.2 Hz, 1H, 5Q), 7.93-7.89 (m, 2H, 3Q, 7Q), 7.76 (t, J=7.8 Hz, 6Q), 7.23 (d, J=8.6 Hz, 1H Ar), 7.10 (d, J=2.6 Hz, 1H Ar), 6.86 (dd, J₁=8.6, J₂=2.3, 1H Ar.), 5.5 (s, 2H, OCH₂-q), 3.91 (m, 2H), 3.51 (s, 3H, OCH₃), 2.91 (d, J=13.7 Hz, 1H), 2.74 (d, J=13.5 Hz, 1H), 2.56 (m, 2H), 1.93 (q, J=7.4 Hz, 2H), 0.60 (t, J=7.2 Hz, 3H, CH₂CH₃).
- 30 IR (KBr) 3400 cm⁻¹, 3200 cm⁻¹ (NH, OH), 1740 cm⁻¹ (C=O).
- Mass: EI (m/e) M⁺ 430, ions 401, 357.

- 45 -

Analysis for: $C_{26}H_{26}N_2O_4 \cdot HCl$

Calculated: C, 66.88; H, 5.83; N, 6.00.

Found: C, 66.58; H, 5.75; N, 5.96.

Example 14

5

1,3,4,9-Tetrahydro-1,1-dimethyl-6-(2-quinolinyl-methoxy)pyrano[3,4-b]indole

A. 1,3,4,9-Tetrahydro-1,1-dimethyl-6-(phenylmethoxy)pyrano[3,4-b]indole

A mixture consisting of 5-benzyloxytryptophol (3.2 g, 0.012 mol), acetone (7 mL), benzene (300 mL) and p-toluene sulfonic acid (500 mg) is refluxed for 3.5 hours using a Dean-Stark trap to remove the water. The reaction mixture is cooled to room temperature and washed with 5% sodium bicarbonate (1 x 200 mL), water (200 mL) and brine (200 mL). It is dried ($MgSO_4$), filtered and concentrated to give 5.0 g product as thick oil. The crude product is flash chromatographed with 15% ethyl acetate/hexane as an eluent to afford 2.5 g product, m.p. 128-129°C.

15 B. 1,3,4,9-Tetrahydro-1,1-dimethyl-6-hydroxy-pyrano[3,4-b]indole

A mixture consisting of 10% Pd/c on charcoal (0.7 g), ethanol (150 mL) and 1,3,4,9-tetrahydro-1,1-dimethyl-6-(phenylmethoxy)pyrano[3,4-b]indole (4.2 g, 0.014 mol) of Step A, is hydrogenated at 30 psi for 18 hours. The reaction mixture is filtered and concentrated to give 3.5 g product which is used in the next reaction without further purification.

C. 1,3,4,9-Tetrahydro-1,1-dimethyl-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole

A mixture consisting of the 6-hydroxy compound (3.5 g, 0.016 mol) of Step B, dimethylformamide (100 mL), potassium carbonate, anhydrous (6.0 g, 0.043 mol), potassium iodide (100 mg) and 2-chloromethylquinoline (2.9 g, 0.016 mol) is heated at 60°C for 24 hours. The reaction mixture is cooled to room temperature, diluted with water (600 mL), and extracted with ethyl acetate (3 x 150 mL). The combined organic layers are washed with 2.5N NaOH, water (2 x 100 mL), once with brine (100 mL), dried ($MgSO_4$), filtered and concentrated to give 3.8 g of crude product. The crude product is flash chromatographed on silica gel using 40% ethyl acetate/hexane as an eluent to afford 2.3 g of product which is recrystallized from methanol to afford 1.69 g pure title compound, m.p. 164-165°C.

1H NMR (400 MHz, DMSO- d_6): δ 10.68 (s, 1H, NH), 8.38 (d, J=8.6 Hz, 1H, 4Q), 8.0 (d, J=8.4 Hz, 1H, 8Q), 7.97 (d, J=8.1 Hz, 1H, 5Q), 7.77 (t,

- 46 -

J=7.1 Hz, 1H, 7Q), 7.69 (d, J=8.6 Hz, 1H, 3Q), 7.59 (t, J=7.1 Hz, 1H, 6Q), 7.18 (d, J=8.7 Hz, 1H Ar), 7.04 (d, J=2.4 Hz, 1H Ar), 6.82 (dd, J₁=8.6, J₂=2.4 Hz, 1H Ar), 5.34 (s, 2H, OCH₂Q), 3.85 (t, J=5.3 Hz, 2H), 2.56 (t, J=5.3 Hz, 2H), 1.44 (s, 6H, (CH₃)₂).

5 IR (KBr): 3410 cm⁻¹ (broad NH).

Mass: EI: m/e: 358 (M⁺), 343 143.

Analysis for: C₂₃H₂₂N₂O₂

Calculated: C, 77.07; H, 6.19; N, 7.81.

Found: C, 76.76; H, 6.25; N, 7.70.

10

Example 15

1,3,4,9-Tetrahydro-1,1-diethyl-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole

A. 1,3,4,9-Tetrahydro-1,1-diethyl-6-(phenylmethoxy)pyrano[3,4-b]indole

15 A mixture consisting of 5-benzyloxytryptophol (7.0 g, 0.0262 mol), diethyl ketone (10 mL), benzene (400 mL) and p-toluene sulfonic acid is refluxed for 3.5 hours using a Dean-Stark tap to remove the water. The reaction mixture is cooled to room temperature, washed with 5% sodium bicarbonate, water (200 mL), brine (200 mL), dried (MgSO₄), filtered and concentrated to give 9.9 g of crude product. The crude product is flash chromatographed on silica gel using 15% ethyl acetate/hexane as an eluent to afford 6.5 g of pure title compound.

20

B. 1,3,4,9-Tetrahydro-1,1-diethyl-6-(hydroxy)pyrano[3,4-b]indole

A mixture consisting of 10% Pd/c on charcoal (1.0 g), ethanol (125 mL), and 1,3,4,9-tetrahydro-1,1-diethyl-6-(phenylmethoxy)pyrano[3,4-b]indole (6.5 g, 0.0193 mol), of Step A, is hydrogenated at 30 psi for 18 hours. The reaction mixture is filtered and concentrated to give 5.2 g of product which is used in the next reaction without further purification.

25

C. 1,3,4,9-Tetrahydro-1,1-diethyl-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole

A mixture consisting of the 6-hydroxy compound (5.2 g, 0.0212 mol) of Step B, dimethyl sulfoxide (150 mL), sodium hydroxide (6.0 g, 0.15 mol in 20 mL water), and 2-chloromethylquinoline hydrochloride (6.0 g, 0.028 mol) is heated to 70-80°C for 6 hours. The reaction mixture is cooled to room temperature, diluted with water (800 mL), and extracted with ethyl acetate (3 x 150 mL). The combined organic layers are washed once with water (2 x 150 mL), once with brine

30

- 47 -

(100 mL), dried (MgSO₄), filtered and concentrated to give 9.9 crude product. The crude product is flash chromatographed on silica gel using 25% ethyl acetate/hexane as an eluent to afford 4.5 g pure product as a thick oil. The oil is dissolved in ether (150 mL) and ether/HCl is added dropwise. The precipitate is filtered off and the product crystallized from methanol/ether to give 2.6 g product as a yellow crystalline solid, m.p. 164-166°C.

¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (s, 1H, NH), 8.70 (d, J=8.6 Hz, 1H, 4Q), 8.21 (d, J=8.5 Hz, 1H, 8Q), 8.13 (d, J=8.1 Hz, 1H, 5Q), 7.95-7.88 (m, 2H, 3 and 7 Q), 7.74 (t, J=7.3 Hz, 1H, 6Q), 7.21 (d, J=8.6 Hz, 1H Ar), 7.08 (d, J=2.4 Hz, 1H Ar), 6.84 (dd, J₁=8.7, J₂=2.4 Hz, 1H Ar.), 5.50 (s, 2H, OCH₂Q), 3.85 (t, J=5.3 Hz, 2H), 2.57 (t, J=5.4 Hz, 2H), 1.80 (m, 4H, CH₂CH₃ 1,1-diethyl), 0.71 (t, J=7.3 Hz, 6H, CH₂CH₃, 1,1-diethyl).

IR: (KBr) 3410 cm⁻¹ (NH).

Mass: EI: M/e: 386 (M⁺) ions 357, 216, 142, 128.

15 Analysis for: C₂₅H₂₆N₂O₂·HCl

Calculated: C, 70.99; H, 6.43; N, 6.62

Found: C, 71.20; H, 6.43; N, 6.66.

Example 16

20 1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid hydrochloride quarter hydrate

A. 2-Methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid, one tenth hydrate

To a previously degassed mixture of dimethylformamide (70 mL) and sodium methoxide/methanol solution (25 wt %, 2 equivalents, 8.8 mL) is added 5-hydroxy-2-methyl-1H-indole-3-acetic acid (4.0 g, 19.5 mmol) at room temperature. After 15 minutes 2-chloromethylquinoline (3.46 g, 19.5 mmol) is added and the mixture stirred overnight. The dimethylformamide is evaporated and the mixture partitioned between pH 4 buffer solution and ethyl acetate. The organic phase is dried (MgSO₄), filtered and partially concentrated. A solid is filtered off and crystallized using ethanol - water. This gives the title compound as a solid (2.96 g), 44% yield, m.p. 208-210°C.

Analysis for: C₂₁H₁₈N₂O₃ · 0.1 H₂O

Calculated: C, 72.44; H, 5.26; N, 8.04.

Found: C, 72.29; H, 5.38; N, 7.93.

- 48 -

B. 2-Methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid methyl ester.

To a stirring mixture of the indole-acetic acid substrate (1.2 g, 3.4 mmol) in tetrahydrofuran (25 mL) is added slowly, a freshly prepared diazomethane/diethyl ether solution at ambient temperature. Upon consumption of starting material, a few drops of acetic acid are added. The solvent is evaporated and methylene chloride is added. This organic phase is washed with water and dried (MgSO₄). Solvent removal gives the product as an oil (1.2 g). Yield is quantitative.

C. 1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid methyl ester

To a stirring mixture of the indole-ester substrate (0.8 g, 2.2 mmol) in dimethylformamide (15 mL) is added sodium hydride (0.058 g, 2.4 mmol). The reaction is stirred for 30 minutes at ambient temperature. 4-Chloro-benzylchloride (0.35 g, 2.2 mmol) is then added. After 2 hours the dimethylformamide is evaporated and the residue partitioned using pH 4 buffer solution and ethyl acetate. The organic phase is separated, dried (MgSO₄) and filtered. Solvent removal produces a solid that is flash chromatographed using chloroform as eluent, then crystallized with acetonitrile to yield the product as a crystalline solid (0.162 g 16% yield) m.p. 132-134°C.

Analysis for: C₂₉H₂₅N₂O₃Cl

Calculated: C, 71.82; H, 5.20; N, 5.78.

Found: C, 71.48; H, 5.17; N, 5.88.

D. 1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid hydrochloride quarter hydrate

The above ester (2.2 g, 4.5 mmol) is combined with tetrahydrofuran (50 mL), 1N NaOH solution (50 mL) and heated to reflux (3.5 hours). The tetrahydrofuran is removed in vacuo and the aqueous phase acidified with 1N HCl. A crude solid is filtered and recrystallized using ethanol to produce 1.16 g of product as the hydrochloride salt (50% yield), m.p. 249-251°C.

Analysis for: C₂₈H₂₃ClN₂O₃ · HCl · 1/4 H₂O

Calculated: C, 65.69; H, 4.82; N, 5.47.

Found: C, 65.64; H, 4.92; N, 5.41.

Example 17

**1-(4-Chlorobenzoyl)-2-methyl-5-(2-quinolinylmethoxy)-
1H-indole-3-acetic acid three quarters hydrate**

A. 1-(4-Chlorobenzoyl)-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid methyl ester one tenth hydrate

To a solution of 2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid methylester (0.95 g, 2.6 mmol) (see Example 16B) in dimethylformamide (10 mL) at 0°C is added sodium hydride (0.12 g, 50% dispersion) and the mixture stirred 20 minutes. 4-Chlorobenzoyl chloride (0.45 g, 2.6 mmol) is then added and the mixture stirred overnight; 100 mL of 5% acetic acid is used to quench the reaction. After extraction with a 1:1 mixture of ether:ethyl acetate, the organic phase is washed with water, saturated NaHCO₃ solution, water and brine. It is then separated and dried (MgSO₄). Solvent removal gives a crude solid which is flash chromatographed using methylene chloride-methanol (99-1) as eluent. The product is isolated and crystallized from acetonitrile (0.20 g, m.p. 117-118°C), yield is 15%.

Analysis for: C₂₉H₂₃ClN₂O₄ · 0.1 H₂O

Calculated: C, 69.55; H, 4.66; N, 5.59.

Found: C, 69.35; H, 4.48; N, 5.56.

B. 1-(4-Chlorobenzoyl)-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid three quarters hydrate

To a mixture of the above ester (0.5 g, 1.0 mmol) in acetonitrile (20 mL) is added iodotrimethyl silane (0.46 g, 2.2 mmol). After refluxing for 24 hours the mixture is diluted with ethyl acetate then washed with 10% Na₂S₂O₃ solution, water and 15% NaHCO₃ solution. A precipitate forms which is filtered off, washed with 1N HCl and dried in vacuo to give the title compound as a solid (0.05 g, 10% yield), m.p. 191-193°C.

Analysis for: C₂₈H₂₁ClN₂O₄ · 0.75 H₂O

Calculated: C, 67.47; H, 4.55; N, 5.62.

Found: C, 67.68; H, 4.22; N, 5.94.

Example 18**2-Methyl-5-(2-quinolinylmethoxy)-1,2-(quinolinyl-
methyl)-1H-indole-3-acetic acid**

To a stirred suspension of sodium hydride (1.4 g, 29.2 mmol) in dimethylformamide (40 mL) at 0°C is added 5-hydroxy-2-methyl-1H-indole-3-acetic acid (2.0 g, 9.76 mmol). After 1 hour 2-chloromethylquinoline (3.44 g, 19.48 mmol) is added and the reaction mixture is allowed to warm to room temperature. After stirring overnight water is added and the pH was adjusted to 5 with 0.5N HCl. The reaction mixture is extracted with methylene chloride, the organic extract is dried over MgSO₄ and evaporated to a solid which upon sequential trituration with ethanol and hot ethanol affords 2.5 g (52%) of a beige solid, m.p. 198-200°C.

Analysis for: C₃₁H₂₅N₃O₃

Calculated: C, 76.37; H, 5.17; N, 8.62.

Found: C, 76.72; H, 5.24; N, 8.74.

Example 19**1-[(4-Chlorophenyl)methyl]-5-(hexyloxy)-
2-methyl-1H-indole-3-acetic acid****A. 5-(Hexyloxy)-2-methyl-1H-indole-3-acetic acid**

To a solution of 5-hydroxy-2-methyl-1H-indole-3-acetic acid (7.17 g, 35.0 mmol) in methanol (40 mL) is added sodium methoxide (70 mmol). The solution is evaporated, dimethylformamide (40 mL) is added followed by hexyl iodide (35.0 mmol). After 2 days the solvent is removed and the residue is partitioned between ethyl acetate and pH=4 buffer. The organic layer is separated, dried over MgSO₄ and evaporated to 8.6 g of a brown solid. Recrystallization from ethanol/water affords 6.23 g (62%) of white crystals, m.p. 65-67°C.

Analysis for: C₁₇H₂₃NO₃

Calculated: C, 70.56; H, 8.01; N, 4.84.

Found: C, 70.52; H, 7.98; N, 4.83.

B. 1-[(4-Chlorophenyl)methyl]-5-(hexyloxy)-2-methyl-1H-indole-3-acetic acid

The acid from part A is converted to the methyl ester (m.p. 148-150°C) via diazomethane (see Example 16B). To a solution of the ester (4.5 g, 14.83 mmol) in dimethylformamide (40 mL) is added sodium hydride (1.42 g, 29.6 mmol). After 30 minutes 4-chlorobenzylchloride (2.38 g, 14.83 mmol) is added. After stirring

- 51 -

overnight, the solvent is removed and the residue is partitioned between ethyl acetate and pH=4 buffer. The organic layer is separated, dried over MgSO_4 and evaporated to a red solid. Sequential recrystallization from ether and isopropanol gives 2.2 g of crystals (36%), m.p. 148-150°C.

- 5 Analysis for: $\text{C}_{24}\text{H}_{28}\text{ClNO}_3$
Calculated: C, 69.64; H, 6.82; N, 3.38.
Found: C, 70.00; H, 6.71; N, 3.46.

Example 20

10 2-Methyl-5-(2-quinolinylmethoxy)-1-(2-quinolinyl-
methyl)-1H-indole-3-carboxylic acid ethyl ester

- Under an atmosphere of nitrogen, a mixture of ethyl-5-hydroxy-2-methyl-3-indolyl carboxylate (3.5 g, 16 mmol), finely powdered anhydrous potassium carbonate (2.2 g, 16 mmol) and 18-crown-6 (0.48 g, 1.8 mmol) in dry acetonitrile (50 mL) is stirred at room temperature for 0.5 hours. In one portion
15 2-chloromethylquinoline (free base, 2.85 g, 16 mmol) is added and the mixture is stirred at 55°C overnight. The reaction (found to be complete by TLC analysis) is filtered hot.

- The filtrate affords the desired product (0.75 g, 9%) as a tan solid, m.p. 162-163°C. Recrystallization from ethyl acetate gives pure product (0.42 g, m.p.
20 162-163°C).

Analysis for: $\text{C}_{32}\text{H}_{27}\text{N}_3\text{O}_3$
Calculated: C, 76.63; H, 5.43; N, 8.3.
Found: C, 76.20; H, 5.59; N, 8.11.

Example 21

25 α -Methyl-6-(2-quinolinylmethoxy)-9-(2-quinolinyl-
methyl)-9H-carbazole-2-acetic acid

A. 4-Benzyloxyphenylhydrazine hydrochloride

- A solution of sodium nitrite (3.8 g, 0.055 mol in 20 mL of H_2O), is added dropwise to an ice cold stirring suspension of 4-benzyloxyaniline (13.0 g, 0.055 mol in 150 mL of concentrated HCl). The reaction mixture is stirred for 90
30 minutes at -8° to 10°C. A solution of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (32.0 g, 0.142 mol in 50 mL concentrated HCl) is added and stirred for 1 hour at 0°C. The reaction mixture is removed from the ice bath and is stirred at room temperature for 20 hours. The mixture

- 52 -

is then filtered and washed with water to give 13.0 g (95% yield) of product, m.p. 182-185°C.

B. 6-Benzoyloxy- α -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester

A mixture containing 4-benzyloxyphenylhydrazine hydrochloride (37.0 g, 0.148 mol), α -methyl-3-oxocyclohexane acetic acid (40.0 g, 0.235 mol), glacial acetic acid (650 mL) and H₂O (100 mL) is stirred at room temperature under a nitrogen atmosphere for 2.5 hours. The mixture is then refluxed for 20 minutes, cooled and poured into 200 mL of ice/H₂O. The precipitate is filtered to give 80 g of red colored crude product.

The crude product is dissolved in ether (600 mL) concentrated H₂SO₄ (5 mL) is added and the mixture refluxed for 24 hours. The reaction mixture is cooled, concentrated and diluted with ether (100 mL), then washed with 1N NaOH (2 x 200 mL), water (2 x 200 mL) and finally once with brine (200 mL), dried over anhydrous MgSO₄, filtered and concentrated to give 40.0 g crude product as a thick oil.

C. 6-Benzoyloxy- α -methyl carbazole-2-acetic acid ethyl ester

A mixture consisting of 6-benzyloxy- α -methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (15.0 g, 0.0398 mol) xylene (500 mL), and chloranil (10.0 g, 0.0408 mol) is refluxed in the dark under a nitrogen atmosphere for 24 hours. The reaction mixture is concentrated to 200 mL and the precipitate is removed by filtration. The precipitate is triturated with benzene (3 x 100 mL), the solvent fractions are combined and washed with 1N NaOH (3 x 150 mL), washed with water until neutral to pH paper, dried over MgSO₄, filtered and concentrated to give 15.8 crude product. The crude product is flash chromatographed on silica gel using 15% ethyl acetate/hexane as an eluent to give 7.5 g product as a thick oil.

D. 6-Hydroxy- α -methyl carbazole-2-acetic acid ethyl ester

A mixture consisting of 6-benzyloxy- α -methyl carbazole-2-acetic acid ethyl ester (7.3 g, 0.0195 mol) and ethanol (130 mL) is subjected to hydrogenation over 10% Pd/c (0.9 g) for 18 hours at 35 psi. The reaction mixture is filtered and concentrated to give 5.0 g product as a foam.

E. 6-Hydroxy- α -methyl carbazole-2-acetic acid

A mixture consisting of 6-hydroxy- α -methyl carbazole-2-acetic acid ethyl ester (5.0 g, 0.021 mol), potassium hydroxide (5.0 g, 0.089 mol), methanol

- 54 -

Analysis for: $C_{29}H_{26}ClN_3O_3 \cdot 3/4 H_2O$
Calculated: C, 67.83; H, 5.39; N, 8.18.
Found: C, 67.87; H, 5.10; N, 8.39.

Example 23

5 **1-[(4-Chlorophenyl)methyl]-2-methyl-N-(phenylsulfonyl)-**
 5-(2-quinolinylmethoxy)-1H-indole-3-acetamide

To a solution of the acid of Example 16 (1.0g, 2.12mmol), benzene-sulfonamide (0.34g, 2.12mmol) and benzotriazole-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (0.94g, 2.12mmol) in methylene chloride(25 mL)
10 is added triethylamine (0.6mL, 2 equiv). The reaction mixture is stirred overnight and then is quenched by addition of brine. After sequential washes with water, 0.5N HCl and water, the organic layer is dried over $MgSO_4$ and evaporated to afford a crude solid, which upon toluene recrystallization affords a crystalline solid, m.p. 194-197°C.

15 Analysis for: $C_{34}H_{28}ClN_3O_4S$
 Calculated: C, 66.93; H, 4.63; N, 6.89.
 Found: C, 67.01; H, 4.66; N, 7.33.

Example 24

20 **1-[(4-Fluorophenyl)methyl]-2-methyl-5-(2-quinolinyl-**
 methoxy)-1H-indole-3-acetic acid hemihydrate

The title compound is prepared according to the method of Example 16 using 4-fluorobenzyl bromide. A crystalline solid is obtained, m.p. 199-202°C.

Analysis for: $C_{28}H_{23}FN_2O_3 \cdot 1/2 H_2O$
Calculated: C, 72.55; H, 5.21; N, 6.04.
25 Found: C, 72.84; H, 5.31; N, 5.68.

Example 25

1-[(4-Bromophenyl)methyl]-2-methyl-5-(2-quinolinyl-
 methoxy)-1H-indole-3-acetic acid hemihydrate

The title compound is prepared according to the method of Example 16
30 using 4-bromobenzyl bromide. A crystalline solid is obtained, m.p. 215-217°C.

- 53 -

(300 mL), and water (20 mL) is refluxed for 15 hours. The reaction mixture is cooled concentrated and acidified with a 1:1 solution of concentrated HCl and water to pH 1. The aqueous layer is extracted with ether (4 x 300 mL), washed with water (200 mL), brine (200 mL), dried over MgSO₄, filtered and concentrated to give 2.6 g of product as a foam.

F. α -Methyl-6-(2-quinolinylmethoxy)-9-(2-quinolinylmethyl)-9H-carbazole-2-acetic acid

A mixture consisting of 6-hydroxy- α -methyl carbazole-2-acetic acid (2.6 g, 0.010 mol), dimethyl sulfoxide (200 mL), sodium hydroxide (2.0 g in 20 mL H₂O, 0.05 mol) and 2-chloromethylquinoline-HCl (4.0 g, 0.018 mol) is heated to 80°C for 3 hours. The reaction mixture is cooled, poured into water (1000 mL), and the pH is adjusted to 4 with 1N HCl. The aqueous solution is extracted with ethyl acetate (4 x 300 mL) and the organic layers are combined, washed with water (2 x 300 mL), once with brine (300 mL), dried over MgSO₄, filtered and concentrated to give 3.0 g of crude product. The latter is chromatographed on silica gel using 10% methanol/methylene chloride as an eluent to give 8 g of product, m.p. 197-199°C.

Analysis for: C₃₅H₂₇N₃O₃

Calculated: C, 78.19; H, 5.06; N, 7.82.

Found: C, 76.01; H, 5.02; N, 7.36.

Example 22

1-[(4-Chlorophenyl)methyl]-2-methyl-N-(methyl)-N-(hydroxy)-5-(2-quinolinylmethoxy)-1H-indole-3-acetamide three quarters hydrate

To a solution of the acid of Example 16 (0.2 g, 0.42mmol), N-methyl-hydroxylamine hydrochloride (0.035 g, 0.42mmol) and benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.188g, 0.42mmol) in methylene chloride (5 mL) is added triethylamine (0.12mL, 2 equiv). The reaction mixture is stirred overnight and then is quenched by addition of brine. After sequential washes with water, 0.5N HCl and water, the organic layer is dried over MgSO₄ and evaporated to afford a crude solid, which upon chloroform recrystallization(twice) affords a crystalline solid, m.p. 192-194°C. This material is washed sequentially with 0.5N NaOH and water and dried to afford white crystals, m.p. 191-193°C.

- 56 -

Example 29**2-Methyl-1-pentyl-5-(2-quinolinylmethoxy)-
1H-indole-3-acetic acid hemihydrate**

5 The title compound is prepared according to the method of Example 16 using pentyl iodide. A crystalline solid is obtained, m.p. 90-93°C.

Analysis for: $C_{26}H_{28}N_2O_3 \cdot 1/2 H_2O$

Calculated: C, 73.38; H, 6.86; N, 6.58.

Found: C, 73.37; H, 7.11; N, 6.41.

Example 30

10 **1-Hexyl-2-methyl-5-(2-quinolinylmethoxy)-1H-
indole-3-acetic acid three quarters hydrate**

The title compound is prepared according to the method of Example 16 using hexyl iodide. A crystalline solid is obtained, m.p. 122-124°C.

Analysis for: $C_{27}H_{30}N_2O_3 \cdot 3/4 H_2O$

15 Calculated: C, 73.03; H, 7.15; N, 6.30.

Found: C, 73.25; H, 7.10; N, 6.30.

Example 31**1-Heptyl-2-methyl-5-(2-quinolinyl-
methoxy)-1H-indole-3-acetic acid**

20 The title compound is prepared according to the method of Example 16 using heptyl iodide. A crystalline solid is obtained, m.p. 127-131°C.

Analysis for: $C_{28}H_{32}N_2O_3$

Calculated: C, 75.65; H, 7.26; N, 6.30.

Found: C, 75.80; H, 7.19; N, 6.26.

25

Example 32**1-Methyl-2-methyl-5-(2-quinolinyl-
methoxy)-1H-indole-3-acetic acid**

The title compound is prepared according to the method of Example 16 using methyl iodide. A crystalline solid is obtained, m.p. 186-188°C.

- 55 -

Analysis for: $C_{28}H_{23}BrN_2O_3 \cdot 1/2 H_2O$
Calculated: C, 64.12; H, 4.61; N, 5.34.
Found: C, 64.40; H, 4.76; N, 5.01.

Example 26

5 **1-[(Phenyl)methyl-2-methyl]-5-(2-quinolinyl-methoxy)-1H-indole-3-acetic acid tenth hydrate**

The title compound is prepared according to the method of Example 16 using benzyl bromide. A crystalline solid is obtained, m.p. 199-202°C.

Analysis for: $C_{28}H_{24}N_2O_3 \cdot 0.1 H_2O$
10 Calculated: C, 76.72; H, 5.56; N, 6.39.
 Found: C, 76.30; H, 5.37; N, 6.34.

Example 27

1-[(4-Carboxyphenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid

15 The title compound is prepared according to the method of Example 16 using 4-(chloromethyl)benzoic acid. A crystalline solid is obtained, m.p. 232-234°C.

Analysis for: $C_{29}H_{24}N_2O_5$
Calculated: C, 72.49; H, 5.03; N, 5.83.
Found: C, 72.44; H, 5.18; N, 5.98.

Example 28

20 **2-Methyl-5-(2-quinolinylmethoxy)-1-[[4-(2-quinolinylmethoxy)-phenyl]methyl]-1H-indole-3-acetic acid hemihydrate**

 The title compound is prepared according to the method of Example 16 using 4-(2-quinolinylmethoxy)benzyl chloride. A crystalline solid is obtained, m.p. 182-185°C.

25 182-185°C.

Analysis for: $C_{38}H_{31}N_3O_4 \cdot 1/2 H_2O$
Calculated: C, 75.73; H, 5.35; N, 6.97.
Found: C, 75.41; H, 5.33; N, 6.78.

- 57 -

Analysis for: $C_{22}H_{20}N_2O_3$
Calculated: C, 73.32; H, 5.59; N, 7.77.
Found: C, 73.03; H, 5.69; N, 7.57.

Example 33

5 **1-[(4-Chlorophenyl)methyl]-5-(2-quinolinyl-
 methoxy)-1H-indole-3-acetic acid**

The title compound is prepared according to the method of Example 16 using 5-hydroxy-1H-indole-3-acetic acid. The desired product is obtained as white crystals, m.p. 158-159°C.

10 Analysis for: $C_{27}H_{21}ClN_2O_3$
 Calculated: C, 70.97; H, 4.63; N, 6.13.
 Found: C, 71.13; H, 4.67; N, 6.03.

Example 34

15 **1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-naphthalenyl-
 methoxy)-1H-indole-3-acetic acid**

The title compound is prepared according to the method of Example 16 using 2-(bromomethyl)naphthalene. A crystalline solid is obtained, m.p. 168-170°C.

Analysis for: $C_{29}H_{24}ClNO_3$
 Calculated: C, 74.12; H, 5.15; N, 2.98.
20 Found: C, 74.43; H, 5.31; N, 2.74.

Example 35

**1-[(4-Chlorophenyl)methyl]-2-methyl-5-
 (phenylmethoxy)-1H-indole-3-acetic acid**

25 The title compound is prepared according to the method of Example 16 using benzyl chloride. A crystalline solid is obtained, m.p. 140-142°C.

Analysis for: $C_{25}H_{22}ClNO_3$
 Calculated: C, 71.51; H, 5.28; N, 3.34.
 Found: C, 71.54; H, 5.29; N, 3.47.

Example 36

1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-pyridinylmethoxy)-1H-indole-3-acetic acid

5 The title compound is prepared according to the method of Example 16 using 2-(chloromethyl)pyridine. A crystalline solid is obtained, m.p. 231-233°C.

Analysis for: C₂₄H₂₁ClN₂O₃

Calculated: C, 68.49; H, 5.03; N, 6.66.

Found: C, 68.61; H, 5.12; N, 6.39.

Example 37

10 **1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-benzothiazolylmethoxy)-1H-indole-3-acetic acid**

A. **2-Methyl-5-(2-benzothiazolylmethoxy)-1H-indole-3-acetic acid ethyl ester**

To a mixture of 5-hydroxy-2-methyl-1H-indole-3-acetic acid ethyl ester (5.6 g, 17.15 mmol) and cesium carbonate (15.0 g, 46.04 mmol) in dimethylsulfoxide (70 mL) that has been previously stirred for 30 minutes is added 2-(chloromethyl)-
15 benzothiazole (4.6 g, 25.08 mmol). After 1 hour the reaction is poured into ice water and extracted with ethyl acetate. The organic layer is washed sequentially with 0.1N NaOH, water and brine, dried over MgSO₄ and evaporated to a black oil which is purified by flash chromatography (eluant: ethyl acetate-hexane) to afford 5.4g (59%) of
20 the alkylated ester.

B. **1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-benzothiazolylmethoxy)-1H-indole-3-acetic acid**

The title compound is prepared according to the method of Example 16 using 2-methyl-5-(2-benzothiazolylmethoxy)-1H-indole-3-acetic acid ethyl ester and 4-chlorobenzyl chloride; however, the hydrolysis is carried out in aqueous methanol.
25 Recrystallization from acetonitrile affords white crystals, m.p. 175-176°C.

Analysis for: C₂₆H₂₁ClN₂O₃S

Calculated: C, 65.47; H, 4.44; N, 5.87.

Found: C, 65.17; H, 4.61; N, 5.81.

Example 38**1-[(4-Chlorophenyl)methyl]-2-methyl-5-[(2-phenyl-4-thiazolyl)methoxyl]-1H-indole-3-acetic acid**

5 The title compound is prepared according to the method of Example 37 using 4-(chloromethyl)-2-phenylthiazole. White crystals are obtained, m.p. 150-151°C.

Analysis for: C₂₈H₂₃ClN₂O₃S

Calculated: C, 66.86; H, 4.61; N, 5.57.

Found: C, 66.46; H, 4.59; N, 5.59.

10

Example 39**1-[(4-Chlorophenyl)methyl]-2-methyl-5-[[2-(4-trifluoromethyl-phenyl)-4-thiazolyl]methoxyl]-1H-indole-3-acetic acid**

15 The title compound is prepared according to the method of Example 37 using 4-chloromethyl-[(4-trifluoromethyl)-2-phenyl]thiazole. White crystals are obtained, m.p. 196-197°C.

Analysis for: C₂₉H₂₂ClF₃N₂O₃S

Calculated: C, 61.00; H, 3.88; N, 4.91.

Found: C, 60.95; H, 3.97; N, 4.89.

20

Example 40**1-[(Phenyl)methyl]-2-methyl-5-[(2-phenyl-4-thiazolyl)methoxyl]-1H-indole-3-acetic acid**

25 The title compound is prepared according to the method of Example 37 using 4-(chloromethyl)-2-phenylthiazole and benzyl chloride. White crystals are obtained from toluene, m.p. 150-151°C.

Analysis for: C₂₈H₂₄N₂O₃S

Calculated: C, 71.77; H, 5.16; N, 5.98.

Found: C, 71.53; H, 5.11; N, 5.90.

Example 41

2-Methyl-5-(2-quinolinylmethoxy)-1-[[4-(2-quinolinylmethoxy)phenyl]methylenel-1H-indene-3-acetic acid

A. 2-Methyl-5-(2-quinolinylmethoxy)-1H-indene-3-acetic acid methyl ester

5 A mixture of 2-methyl-5-hydroxy-1H-indene-3-acetic acid methyl ester (1.8 g, 8.25 mmol), powdered anhydrous potassium carbonate (1.13 g, 8.25 mmol) and 18-crown-6 (0.219 g) in acetonitrile (21 mL) is stirred at room temperature for 15 minutes. 2-(Chloromethyl)quinoline (1.6 g, 9.08 mmol) is then added and the mixture is stirred for 15 hours at 65°C. After the solvent is removed, the residue is partitioned
10 between water and ethyl acetate. The organic phase is dried over MgSO₄ and evaporated. The crude product is purified by flash chromatography (eluant: methylene chloride-ethyl acetate) to afford 2.35 g (79%) of the desired product.

B. 2-Methyl-5-(2-quinolinylmethoxy)-1-[[4-(2-quinolinylmethoxy)phenyl]methylenel-1H-indene-3-acetic acid

15 To a solution of the above ester (1.77 g, 4.93 mmol) in anhydrous methanol (20 mL) is added 4-[(2-quinolinyl)methoxy]benzaldehyde (1.63 g., 6.19 mmol) followed by dropwise addition of 25% methanolic sodium methoxide(3.46 mL). After the reaction mixture is refluxed for 13 hours, the solvent is removed and water is added. The pH is adjusted to 6.5 and the resulting precipitate is extracted sequentially
20 with methylene chloride and ethyl acetate. The combined extracts are dried over MgSO₄ and evaporated to a crude solid which is triturated with diethyl ether and then redissolved in hot ethyl acetate. After the insolubles are filtered off, the solution is concentrated until precipitation occurs. The precipitate is filtered, washed diethyl ether and hexane and dried to afford 1.31 g(45%) of the desired product as a Z/E mixture
25 (7.6/1), m.p. 191-193°C(dec.).

Analysis for: C₃₉H₃₀N₂O₄

Calculated: C, 79.30; H, 5.12; N, 4.74.

Found: C, 79.11; H, 5.05; N, 4.59.

Example 42**N-[[1-[(4-Chlorophenyl)methyl]-2-methyl-5-(2-quinolinyl-methoxy)-1H-indol-3-yl]methyl]-N'-hydroxyurea**

To a solution of the acid of Example 16 (0.72 g, 1.52 mmol), in
5 benzene (25 mL) is added triethylamine (0.23 mL, 1.1 equiv) followed by diphenyl-
phosphoryl azide (0.46 g, 1.1 equiv). After the reaction mixture is heated at 90°C for 1
hour, a solution of hydroxylamine hydrochloride (0.23 g, 2.2 equiv.) in a mixture of
triethylamine (0.46 mL) and water (0.25 mL) is added to it, and the reaction mixture is
10 heated at 90°C overnight. The reaction is quenched by addition of ammonium chloride
solution, and the resulting precipitate is filtered off, washed with water and ethyl acetate
and dried to afford 0.45 g (59%) of a white solid, m.p. 184-186°C.

Analysis for: C₂₈H₂₅ClN₄O₃

Calculated: C, 67.13; H, 5.03; N, 11.18.

Found: C, 66.85; H, 5.06; N, 10.85.

15

Example 43

The compounds 5- and 12-hydroxyeicosatetraenoic acid (5-HETE and
12-HETE) and LTB₄ are early arachidonic acid oxidation products in the lipoxygenase
cascade, which have been shown to mediate several aspects of inflammatory and aller-
gic response. This is especially true with respect to 5,12-diHETE, which is also
20 denoted as LTB₄ [see Ford-Hitchinson, *J. Roy. Soc. Med.*, 74, 831 (1981)]. Com-
pounds which inhibit the PLA₂-mediated release of arachidonic acid thereby effectively
prevent the oxidation of arachidonic acid to the various leukotriene products via the
lipoxygenase cascade. Accordingly, the specificity of action of PLA₂ inhibitors can be
determined by the activity of test compounds in this assay, which measures the ability
25 of compounds to inhibit the synthesis of LTB₄ by rat glycogen-elicited polymorpho-
nuclear leukocytes (PMN) in the presence of exogenous substrate.

The assay is carried out as follows:

Rat polymorphonuclear leukocytes (PMNs) are obtained from female Wistar
rats (150-200 g) which receive an injection of 6% glycogen (10 ml i.p.). Rats are
30 sacrificed 18-24 hours post injection by CO₂ asphyxiation and the elicited cells are
harvested by peritoneal lavage using physiological saline (0.9% NaCl). The exudate is
centrifuged at 400 xg for 10 minutes. The supernatant fluid is discarded and the cell

- 62 -

pellet is resuspended to a concentration of 2.0×10^7 cells/mL in HBSS containing Ca^{++} and Mg^{++} and $10 \mu\text{M}$ L-cysteine.

- 5 To 1 mL aliquots of cell suspension, test drugs or vehicle are added, then preincubated at 37°C for 10 minutes. A23187 ($1 \mu\text{M}$), $[\text{^3H}]$ -AA ($3.0 \mu\text{Ci/mL}$) and unlabeled AA ($1 \mu\text{M}$) are then added and the samples are further incubated for 10 minutes. The reaction is terminated by centrifugation and pelleting cells. Supernatants are then analyzed by HPLC analysis on a $15 \text{ cm} \times 4.6 \text{ mm ID}$ supelcosil LC-18 (Supelco)(3M) column, using a two solvent system at a flow rate of 1.4 mL total flow as follows:

- 10 Solvent A: 70:30 $17.4 \text{ mM H}_3\text{PO}_4$: CH_3CN
 Solvent B. CH_3CN
 Gradient: (system is equilibrated with Solvent A)

	<u>Time</u>	<u>Percent A</u>	<u>Percent B</u>
	0	100	0
15	15.0	100	0
	20.0	65	35
	40.0	65	35
	42.0	10	90
	50.0	10	90
20	50.1	100	0

Percent solvent changes are accomplished in a linear fashion.

- Injections: 140 μL of each supernatant is injected directly onto column and ^3H arachidonic acid metabolites are monitored using an on-line radioactivity detector (Ramona, IN/US, Fairfield, NJ).
- 25 Standards: $10^4 - 2.0 \times 10^4$ dpm of eicosanoids of interest are injected in $90 \mu\text{L}$ EtOH cocktail.

Co-chromatography with standard $[\text{^3H}]$ leukotriene B_4 (LTB_4) in medium of stimulated PMN exposed to drug is compared to that found in medium of stimulated cells exposed to no drug, generating percent inhibition.

- 30 Results are expressed as percent inhibition at a given compound dose or as an IC_{50} value.

Testing compounds of the invention in this assay gave the following results:

- 63 -

Table I

	<u>Compound of Example No.</u>	<u>% Inhibition</u>
5	carprofen	-10* (at 10 μ M)
	etodolac	21 (at 0.5 μ M)
	indomethacin	31 (at 10 μ M)
	sulindac	-10* (at 10 μ M)
10	1	96 (at 10 μ M)
	2	96 (at 10 μ M)
	4	92 (at 0.5 μ M)
	8	91 (at 10 μ M)
	9	96 (at 10 μ M)
	10	91 (at 10 μ M)
	11	95 (at 10 μ M)
15	14	91 (at 10 μ M)
	16	96 (at 10 μ M)
	16C	88 (at 0.5 μ M)
	17	46 (at 0.5 μ M)
	17A	96 (at 10 μ M)
20	18	88 (at 0.5 μ M)
	20	92 (at 10 μ M)
	21	92 (at 10 μ M)
	24	97 (at 10 μ M)
	25	93 (at 10 μ M)
	26	85 (at 10 μ M)
25	29	88 (at 10 μ M)
	30	90 (at 10 μ M)
	31	85 (at 10 μ M)
	41	100 (at 10 μ M)

30 * negative number denotes potentiation

Example 44

The procedure of Example 43 is also employed for the determination of the extent to which compounds of the invention inhibit the synthesis of the arachidonic acid cyclooxygenase oxidation product PGE₂.

- 64 -

In this assay, the procedure of Example 43 is carried out as described. However, in order to determine cyclooxygenase activity, the samples are co-chromatographed with authentic reference [^3H]-PGE₂.

The results are calculated as in Example 43 and presented below:

5

Table II

	<u>Compound of Example No.</u>	<u>% Inhibition</u>
	carprofen	83 (at 10 μM)
	etodolac	100 (at 0.5 μM)
10	indomethacin	100 (at 10 μM)
	sulindac	23 (at 10 μM)
	1	81 (at 10 μM)
	2	92 (at 10 μM)
	4	7 (at 0.5 μM)
15	8	47 (at 10 μM)
	9	75 (at 10 μM)
	10	-41* (at 10 μM)
	11	80 (at 10 μM)
	14	-48* (at 10 μM)
20	16	* (at 10 μM)
	16C	* (at 10 μM)
	17	60 (at 0.5 μM)
	17A	50 (at 10 μM)
	18	-31* (at 0.5 μM)
25	20	* (at 10 μM)
	21	-94* (at 10 μM)
	24	-126* (at 10 μM)
	25	-67* (at 10 μM)
	26	-125* (at 10 μM)
30	29	-123* (at 10 μM)
	30	-130* (at 10 μM)
	31	-145* (at 10 μM)
	41	-21* (at 0.5 μM)

* Denotes a potentiation of cyclooxygenase (PGE₂ synthesis).

- 65 -

Example 45

The compounds of the invention are tested in an in vitro isolated phospholipase A₂ assay to determine the ability of the test compounds to inhibit the release of arachidonic acid from an arachidonic acid-containing substrate by the action of phospholipase A₂ enzyme from human and non-human sources.

This assay is carried out as follows:

Into a 15 mL polypropylene tube are added the following:

	<u>Agent</u>	<u>Volume, μL</u>	<u>Final Conc.</u>
	³ H-AA <u>E. coli</u> substrate ¹	25	5 nmoles PL
10	CaCl ₂ (0.1M) ²	5	5 mM
	Tris-HCl (0.5M) pH 7.5 ³	20	100 mM
	Water ⁴	25	
	Drug/vehicle ⁵	1	50 μ M
15	PLA ₂	25	Volume yielding 12% hydrolysis in 10 min.
		<hr/> 100	

* pre-incubate at room temperature 30 min prior to substrate addition.

¹ Prepared by adding 2 mL deionized and distilled water to 2 mL ³H-arachidonate. labeled E. coli (lower count), to which is added 1 mL of ³H-arachidonate labeled E. coli (higher count) to yield a total of 5 m substrate (containing 1000 nmoles phospholipid).

² Stock 0.1 m CaCl₂, required for enzyme activity.

³ Stock 0.5 m Trisma-Base.

Stock 0.5 M Trisma-HCl. Adjust pH to 7.5 (optimum for enzyme).

⁴ Deionized and distilled water.

⁵ Stock 10 mM prepared in dimethyl sulfoxide. Make 1:2 dilution with dimethyl sulfoxide and add 1 μ L to 100 μ L assay tube.

⁶ Two human PLA₂ enzymes are used:

a) Semi-purified human platelet acid extract PLA₂ (in 10 mM sodium acetate buffer, pH 4.5). Remove protein precipitate by centrifugation at about 2200 rpm for 10 minutes.

b) Purified human synovial fluid.

Incubate the 100 μ L reaction mixture for 10 minutes at 37°C in a shaking water bath. The reaction is terminated by the addition of 2 mL tetrahydrofuran, followed by

- 66 -

vortexing. NH_2 columns (100 $\mu\text{g/mL}$ - Analytichem International) are conditioned with 0.5 mL tetrahydrofuran followed by 0.5 mL tetrahydrofuran/water (2 mL:0.1 mL, v/v).

The sample is loaded onto the columns and slowly drawn through them. The hydrolyzed arachidonic acid retained in the columns is eluted therefrom with 1 mL tetrahydrofuran/glacial acetic acid (2%). The arachidonic acid is transferred to scintillation vials and quantitated by β -counting analysis. A "total counts" sample is prepared by pipetting 25 μL ^3H -arachidonate *E. coli* directly into a scintillation vial to which is added 1 mL tetrahydrofuran. 10 mL aquasol (scintillation cocktail) is added to all samples.

Calculations:

$$\% \text{ hydrolysis} = \frac{[3\text{H}]AA \text{ dpm (sample)} - [3\text{H}]AA \text{ dpm (nonspecific hydrolysis)}}{\text{total counts dpm}} \times 100$$

$$\% \text{ change} = \frac{\text{vehicle dpm} - \text{drug dpm}}{\text{vehicle dpm}} \times 100$$

Activity of Standard Drugs:

Drug	<u>IC₅₀ (μM)</u>	
	Human Platelet	Human Synovial
	<u>PLA₂</u>	<u>PLA₂</u>
Arachidonic Acid	8.6	3.2
Monoalide	25.2	0.14

When tested in this assay, the compounds of the invention gave the following results:

Table III				
Compound of Example No.	<u>% Inhibition at 10 μM</u>		<u>IC₅₀ (μM)</u>	
	<u>HP*</u>	<u>HSF**</u>	<u>HP</u>	<u>HSF</u>
25 sulindac	33	34		30.2
indomethacin		38 (at 50 μM)		144.8
1			—	9.7
2				3.6
30 4	58	48		
16		46		4.1
17		58		14.9
18	47	30		27.0

- 67 -

Table III (cont'd.)

	Compound of Example No.	% Inhibition at 10 μ M		IC ₅₀ (μ M)	
		HP*	HSF**	HP	HSF
5	19	71	45		
	23		64		
	24		56		
	25		11		
	26		92		2.6
10	27		45		
	28		41		
	29		53		15.5
	30		46		16.4
	31		32		
15	32		36		
	33		38		
	34				33.7
	35		28		52.9
	36		46		
20	37		39		
	38		31		
	39		46		
	40		42		
	41		90		3.8
25	* human platelet				
	** human synovial fluid				

Example 46

The ability of the compounds of the invention to inhibit paw edema induced by the exogenous administration of PLA₂ is measured in the in vivo PLA₂ murine paw edema assay.

The assay is carried out as follows:

Non-fasted, male CD-1 mice (8 weeks old; 31-36 grams) are placed in plastic boxes in groups of six. The right hind paw volume is measured using mercury plethysmography (zero time). Compounds are dosed orally (0.5 mL of 0.5% Tween-80) 1 or 3 hours prior to PLA₂ injection or intravenously (0.2 mL in 0.3%

- 68 -

dimethylsulfoxide/saline) 3 minutes prior to PLA₂ injection. A solution of purified PLA₂, from the diamond back cotton mouth snake (*A. piscivorus piscivorus*) is prepared in saline at a concentration of 6 µg/mL. Fifty (50) µL (0.3 µg) of this PLA₂ solution is injected subcutaneously into the right hind paw with a plastic 1 mL plastic syringe (27 gauge, 1" needle). Paw volume of the injected paw is measured again at 10 minutes, 30 minutes and 60 minutes after PLA₂ injection. Animals are euthanized with CO₂ at the completion of the study.

The paw edema is calculated by subtracting the zero time volume from the volume recorded at each time period. Mean paw edema for each treatment group is then calculated and expressed as (µL ± S.E.). Drug effects are expressed as a percent change from control (vehicle) values. Statistical significance is determined by a one-way analysis of variance with LSD comparison to control (p < 0.05). ED₅₀'s are determined using repression analysis.

The activity of standard drugs in this assay is as follows:

Compound	ED ₅₀ mg/kg p.o. at +10 min.
Cyproheptadine	3.1
BW755C	50
Dexamethasone*	10
Naproxen	18
Aristolochic Acid **	Not Active
Luffarrellolide **	Not Active

* p.o. - 3 hr.

** Some activity (30% inhibition) only when co-injected with enzyme.

When tested in this assay, the compounds of the invention gave the following results:

		Table IV		
		% Change in Edema		
Compound of Example No.	Dose mg/kg	10 min	30 min	60 min
indomethacin	10 (p.o.)**	-32	-31	-42
1	10 (i.v.)*	-6	-9	-40
	100 (p.o.)	+4	-27	-6
2	10 (i.v.)	-39	-43	-37
35	100 (p.o.)	-6	-22	+18
18	30 (i.p.)***		-19	

- 69 -

19	30 (i.p.)	-30
	60 (i.p.)	-34
	* intravenous	
	** peroral	
5	*** intraperitoneal	

The results show that the compounds of the invention are effective in vivo in inhibiting edema induced by the exogenous administration of snake venom PLA₂.

Example 47

10 The compounds of the invention are evaluated for their ability to inhibit the lipoygenase and/or cyclooxygenase pathways of arachidonic acid metabolism in the in vivo murine zymosan peritonitis assay.

This assay is carried out as follows:

Male CD-1 mice (8 weeks old) are placed in plastic boxes in groups of six.
15 Animals are injected with 1 mL i.p. of either 1% zymosan in pyrogen free 0.9% saline or saline (unstimulated control). Compounds are dosed orally 1 hour prior to zymosan injection. Twenty minutes after zymosan injection, the mice are asphyxiated by CO₂ inhalation and the peritoneal cavity is lavaged with 2 mL ice cold Hanks Balanced Salt Solution (HBSS) without CaCl₂, MgSO₄ · 7H₂O and MgCl₂ · 6H₂O. Peritoneal
20 lavage fluid from each mouse is removed by syringe and placed in 5 mL plastic test tubes put on ice and volume is noted. Preparation of samples for evaluation by ELISA is as follows: Samples are centrifuged at 800 xg for 15 minutes; 1 mL of the supernatant is added to 8 mL ice cold methanol and kept at -70°C overnight to precipitate protein; and samples are then centrifuged at 800 xg for 15 minutes, followed
25 by a drying procedure in a Savant speed vac concentrator. The samples are reconstituted with 1 mL ice cold ELISA buffer and stored at -70°C until assayed. The assay for eicosanoids (LTC₄ and 6-keto-PGF_{1α}) is performed according to conventional ELISA procedures.

Compounds to be tested orally are suspended in 0.5% Tween 80.
30 Compounds to be tested intraperitoneally are suspended in 0.5% methylcellulose in 0.9% saline.

The total metabolite level in lavage fluid/mouse is calculated and the significance is determined by a one-way analysis of variance with LSD comparisons to control ($p \leq 0.05$). Drug effects are expressed as a percent change from control values.

- 70 -

The activity of standard drugs in this assay is as follows:

<u>Compound</u>	<u>ED₅₀ mg/kg p.o.</u>	
	<u>LTC₄</u>	<u>6-keto-PGF_{1α}/TxB₂</u>
BW755C	<10	22.0
5 Phenidone	24.0	<30.0
Indomethacin	Not Active	0.126
Ibuprofen	Not Active	7.0

When tested in this assay a compound of the invention and the anti-inflammatory compound etodolac gave the following results:

10 Table V

<u>Compound of Example No.</u>	<u>Dose mg/kg</u>	<u>% Inhibition</u>	
		<u>LTC₄</u>	<u>6-keto-PGF</u>
indomethacin	10 (p.o.) *	+25	
15 10	50 (p.o.)	11	-5 **
11	50 (p.o.)	-49 **	47

* perorally administered

** negative values denote potentiation

20 The results show that the compounds of the invention exert an inhibitory effect on both the lipoxigenase pathway and the cyclooxygenase pathway.

Example 48

The LTD₄ antagonist activity of the compounds of the invention is assessed in the in vitro isolated guinea pig trachea assay.

25 This assay is carried out as follows:

Male Hartley guinea pigs (350-400 g) are euthanized by a blow to the head, the neck is opened and the trachea removed. The trachea is maintained in aerated physiological salt solution, cleared of connective tissue and fat and cut into rings approximately 2 mm in width (usually containing two cartilaginous segments per ring).
 30 Two pieces of silk suture are then passed through the lumen of the tracheal ring and are tied around the cartilage, one on each side of the trachealis muscle. The tracheal ring is suspended between a glass hook and a force displacement transducer in a 10 mL organ bath for measurement of isometric tension. Tissues are maintained at 37°C in aerated

- 71 -

(95% CO₂/5% CO₂) physiological salt solution of the following composition: NaCl (100 mM), KH₂PO₄ (1.18 mM), KCl (4.74 mM), CaCl₂ (2.5 mM), MgSO₄ · 7 H₂O (1.19 mM), NaHCL₃(25 mM), dextrose (11.1 mM) and indomethacin (1 µM). The tracheal rings are maintained at 2 g resting tension and equilibrated for 45 minutes (with frequent washing and readjustment of resting tension).

The tracheal rings are first contracted by the addition of carbachol (3x10⁻⁶M), to determine tissue responsiveness and establish a reference contraction. On attainment of a stable level of contraction (approximately 30 minutes), the tissues are washed several times until baseline tension has been restored and then re-equilibrated for 30 minutes. The tissues are then incubated for 45 minutes with a test antagonist (either 1x10⁻⁶M or 1x10⁻⁵M) or 10 µL of an appropriate solvent control (control, non-treated). One tissue in each group serves as the control. Twenty minutes prior to the construction of the LTD₄ cumulative concentration-response curve, L-cysteine (1x10⁻²M final bath concentration) is added to inhibit bioconversion of LTD₄ to LTE₄. Only one LTD₄ concentration-response curve is constructed in each tissue.

All responses to LTD₄ in an individual tissue are measured as a percentage of the reference contraction of that tissue to carbachol. LTD₄ antagonist activity is determined by comparison of the concentration response curves of LTD₄ in the presence and absence of antagonist. Assessment of the relative rightward shift of the antagonist treated curve relative to the solvent (control) treated tissue is calculated as a concentration ratio (Eq. A) and used in subsequent calculations to derive an antagonist pK_B value (Eqs B and C). In the event that the maximum response to LTD₄ is depressed, the EC₅₀ for that particular curve is determined, an "apparent" pK_B reported, and the compound reported as "non-competitive."

$$A) \text{ Concentration Ratio (CR)} = \frac{EC_{50} \text{ treated tissue}}{EC_{50} \text{ control}}$$

$$B) K_B = \frac{[\text{Test Compound}]}{CR-1}$$

$$C) -\log K_B = pK_B$$

If a compound is found to be active and/or depress the maximal response to LTD₄, then a range of concentrations of the test compound should be used generating multiple concentration ratios which would then be used to perform a Schild analysis, and determination of a pA₂ value where appropriate.

- 72 -

The activity of reference leukotriene antagonists in this assay is as follows:

	<u>Compound</u>	<u>pK_B</u>
	Ly-171,883	7.44 ± 0.12
5	Wy-48,252	6.90 ± 0.23

When tested in this assay, a compound of the invention gave the following results:

	<u>Table VI</u>		
10	<u>Compound of Example No.</u>	<u>pK_B</u>	<u>Concentration Ratio (M)</u>
	9	6.26 ± 0.28	1 x 10 ⁻⁵
	18	5.85 ± 0.12	1 x 10 ⁻⁵

The above results demonstrate that the compounds tested have significant leukotriene antagonist activity as measured in the in vitro isolated guinea pig trachea assay.

Example 49

The compounds of the invention are further tested in the rat carrageenan paw edema assay to determine their ability to inhibit the acute inflammatory response.

This assay is carried out as follows:

20 140-180 g Male Sprague-Dawley rats, in groups of 6 animals are injected subcutaneously in the right paw with 0.1 mL of 1% carrageenan at zero time. Mercury plethysmographic readings (mL) of the paw are made at zero time and 3 hours later. Test compounds are suspended or dissolved in 0.5% methylcellulose and given perorally 1 hour prior to carrageenan administration.

25 The increase in paw volume (edema in mL) produced by the carrageenan is measured. Paw edema is calculated (3 hour volume minus zero time volume), and percent inhibition of edema is determined. Unpaired Student's t-test is used to determine statistical significance.

The activity of standard drugs in this assay is as follows:

30	<u>Drug</u>	<u>Oral ED₅₀ (95% C.L.) mg/kg</u>
	Indomethacin	3.7 (0.6, 23.8)
	Aspirin	145.4 (33.1, 645.6)
	Phenylbutazone	26.2 (2.3, 291.0)

- 73 -

When tested in this assay, a compound of the invention and the anti-inflammatory drug etodolac gave the following results:

Table VII

5	<u>Compound of Example No.</u>	<u>Dose *</u> <u>(mg/kg)</u>	<u>% Inhibition</u> <u>50 mg/kg (peroral)</u>	<u>Oral ED₅₀</u> <u>mg/kg</u>
	etodolac			23
	10	50	48	
	11	50	+1	
	14	50	27	
10	* administered perorally			

The results show that the compounds tested have activity in the rat carrageenan paw edema assay, evidencing an effect on the acute inflammatory response.

Example 50

15 The assay of this Example measures the ability of the compounds tested to inhibit 5-lipoxygenase in human whole blood.

 This assay is carried out as follows:

 Blood is obtained in 50-100 ml quantities from male donors. White blood cell counts and differentials are made. Two ml of blood are placed in a 15 ml
20 polypropylene test tube. Compounds are solubilized in dimethylsulfoxide and diluted 1:10 in 10% bovine serum albumin in phosphate buffered saline, pH 7.4 resulting in a final dimethylsulfoxide concentration of 0.1% in the blood. Then, compounds are added to the blood in a shaking water bath at 37°C for 10 minutes prior to the addition of 30 µM calcium ionophore (A23187; Sigma). After ionophore administration, whole
25 blood samples are mixed and incubated for 20 minutes at 37°C in a shaking water bath. Incubation is terminated by placing samples in an ice bath and immediately adding ethylene glycol-bis-(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (10 mM). Samples are mixed and centrifuged at 1200 x g for 15 minutes at 4°C. Preparation of samples for evaluation by RIA or ELISA is carried out by the following protocol.
30 Plasma is removed from sample tubes, placed in 15 ml polypropylene test tubes containing 8 ml methanol, and then vortexed to precipitate protein. Samples are stored at -70°C overnight. The next day, samples are centrifuged at 200 x g for 15 minutes at 4°C to pellet the precipitate. Samples are dried in a Savant speed vac concentrator,

- 74 -

reconstituted to original volume with ice cold RIA or ELISA buffer, and stored at -70°C until assayed. The assay for eicosanoids (LTB₄, TxB₂, and PGE₂) is performed as described by the manufacturer of the [³H]-RIA kit or ELISA kit (LTB₄-Amersham, TxB₂ and PGE₂ - Caymen Chemical).

5 The total eicosanoid level in 2 ml of blood is calculated and reported as ng/10⁶ neutrophils. Significance is determined by a one-way analysis of variance with least significant difference (LSD) comparisons to control ($p \leq 0.05$) and IC₅₀'s (μ M) are determined by regression analysis (Finney, 1978). Drug effects are expressed as percent change from control values.

10 Compounds tested in vitro are solubilized in dimethylsulfoxide and diluted 1:10 in 10% bovine serum albumin in phosphate buffer saline resulting in a final dimethylsulfoxide concentration of 0.1% in the blood.

The results for compounds of the invention tested in this assay are presented in Table IX.

15

Table VIII

	<u>Compound of Example No.</u>	<u>Dose (μM)</u>	<u>% Inhibition of LTB₄</u>
	A-64077	5	72
	L-663,536	3	96
20	22	25	78

- 75 -

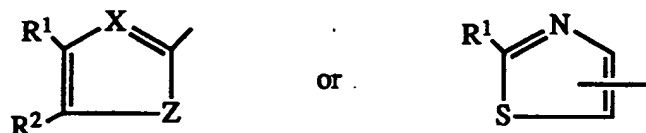
WHAT IS CLAIMED IS:

1. A compound having the formula



wherein

- 5 A is C₄-C₈ alkyl, phenoxyethyl, phenoxyphenyl or a group having the formula



wherein

X is -N- or -C-;

Z is -C(=C)-, -C(=N)-, -N=C-, -N-, -S- or -O-;

- 10 R¹ is hydrogen, lower alkyl, phenyl or phenyl substituted with trifluoromethyl;

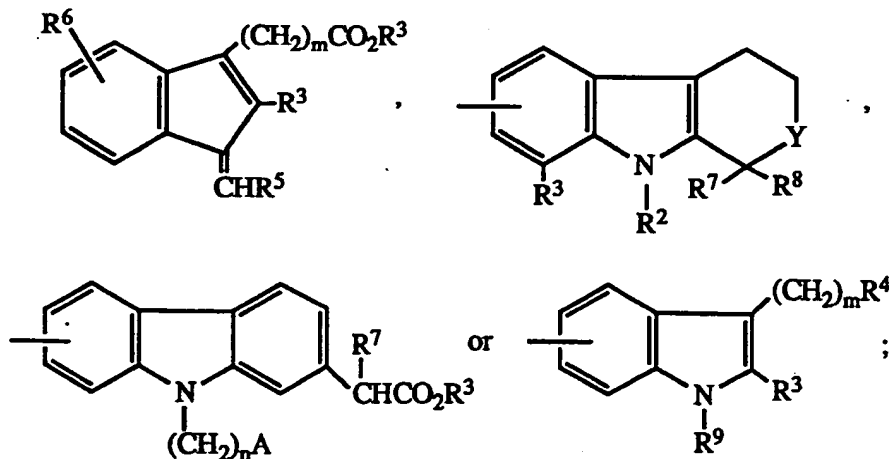
R² is hydrogen or lower alkyl; or

R¹ and R² taken together form a benzene ring;

R³ is hydrogen or lower alkyl;

- 15 n is 1 - 2;

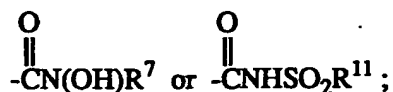
B is



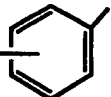
wherein

- 20 R⁴ is -CO₂R², -N(OH)C(=O)NH₂, -N(OH)C(=O)R⁷, -NHC(=O)NHOH,

- 76 -

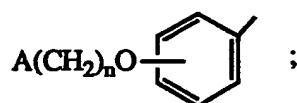
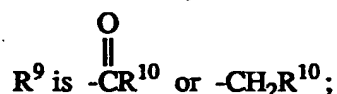


m is 0 - 3;

R^5 is $\text{A}(\text{CH}_2)_n\text{O}-$  ; or phenyl or phenyl substituted by

halo, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl;

R^6 is $\text{A}(\text{CH}_2)_n\text{O}-$ or halo; with the proviso that when R^6 is halo, R^5 is

 R^7 is lower alkyl;Y is $-\text{CH}_2-$ or $-\text{O}-$; R^8 is lower alkyl or $-(\text{CH}_2)_m\text{CO}_2\text{R}^3$;

R^{10} is lower alkyl, phenyl, phenyl substituted with carboxy, halo, loweralkylthio or loweralkylsulfinyl, pyridyl, furanyl or quinoliny;

 R^{11} is lower alkyl or phenyl;

and the pharmacologically acceptable salts thereof.

2. The compound of Claim 1, 3-[(4-chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid.

3. The compound of Claim 1, 2-methyl-3-[[4-(methylthio)phenyl]-methylene]-6-(2-quinolinylmethoxy)-3H-indene-1-acetic acid.

4. The compound of Claim 1, 2-methyl-3-[[4-(methylsulfinyl)phenyl]-methylene]-6-(2-quinolinylmethoxy)-3H-indene-1-acetic acid.

5. The compound of Claim 1, 5-fluoro-2-methyl-1-[[4-(2-quinolinylmethoxy)phenyl]methylene]-1H-indene-3-acetic acid.

6. The compound of Claim 1, 2-methyl-3-[[4-(methylthio)phenyl]-methylene]-6-[(2-naphthyl)methoxy]-3H-indene-1-acetic acid.

7. The compound of Claim 1, 3-[(4-chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid.
8. The compound of Claim 1, 3-[(4-chlorophenyl)methylene]-[2-methyl-6-(2-quinolinylmethoxy)]-3H-indene-1-acetic acid methylester.
- 5 9. The compound of Claim 1, 1,8-diethyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid.
- 10 10. The compound of Claim 1, 1-ethyl-1,3,4,9-tetrahydro-6-(quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid.
11. The compound of Claim 1, 1-methyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid.
12. The compound of Claim 1, 1-ethyl-2,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)-1H-carbazole-1-acetic acid.
13. The compound of Claim 1, 1,3,4,9-tetrahydro-1-propyl-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid.
- 15 14. The compound of Claim 1, 1-ethyl-1,3,4,9-tetrahydro-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole-1-acetic acid, methyl ester.
15. The compound of Claim 1, 1,3,4,9-tetrahydro-1,1-dimethyl-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole.
16. The compound of Claim 1, 1,3,4,9-tetrahydro-1,1-diethyl-6-(2-quinolinylmethoxy)pyrano[3,4-b]indole.
- 20 17. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
18. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid methyl ester.
- 25 19. The compound of Claim 1, 1-(4-chlorobenzoyl)-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.

- 78 -

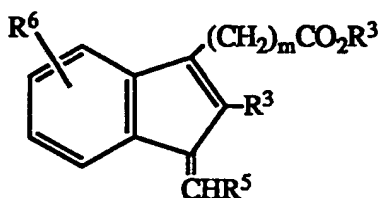
20. The compound of Claim 1, 1-(4-chlorobenzoyl)-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid methyl ester.
21. The compound of Claim 1, 2-methyl-5-(2-quinolinylmethoxy)-1,2-(quinolinylmethyl)-1H-indole-3-acetic acid.
- 5 22. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-5-(hexyloxy)-2-methyl-1H-indole-3-acetic acid.
23. The compound of Claim 1, 2-methyl-5-(2-quinolinylmethoxy)-1-(2-quinolinylmethyl)-1H-indole-3-carboxylic acid ethyl ester.
24. The compound of Claim 1, α -methyl-6-(2-quinolinylmethoxy)-9-(2-quinolinylmethyl)-9H-carbazole-2-acetic acid.
- 10 25. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-N-(methyl)-N-(hydroxy)-5-(2-quinolinylmethoxy)-1H-indole-3-acetamide.
26. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-N-(phenylsulfonyl)-5-(2-quinolinylmethoxy)-1H-indole-3-acetamide.
- 15 27. The compound of Claim 1, 1-[(4-fluorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
28. The compound of Claim 1, 1-[(4-bromophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
29. The compound of Claim 1, 1-[(phenyl)methyl-2-methyl]-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
- 20 30. The compound of Claim 1, 1-[(4-carboxyphenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
31. The compound of Claim 1, 2-methyl-5-(2-quinolinylmethoxy)-1-[[4-(2-quinolinylmethoxy)phenyl]methyl]-1H-indole-3-acetic acid.
- 25 32. The compound of Claim 1, 2-methyl-1-pentyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.

33. The compound of Claim 1, 1-hexyl-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
34. The compound of Claim 1, 1-heptyl-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
- 5 35. The compound of Claim 1, 1-methyl-2-methyl-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
36. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-5-(2-quinolinylmethoxy)-1H-indole-3-acetic acid.
- 10 37. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-naphthalenylmethoxy)-1H-indole-3-acetic acid.
38. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(phenylmethoxy)-1H-indole-3-acetic acid.
39. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-pyridinylmethoxy)-1H-indole-3-acetic acid.
- 15 40. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-benzothiazolylmethoxy)-1H-indole-3-acetic acid.
41. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-[(2-phenyl-4-thiazolyl)methoxy]-1H-indole-3-acetic acid.
- 20 42. The compound of Claim 1, 1-[(4-chlorophenyl)methyl]-2-methyl-5-[[2-(4-trifluoromethylphenyl)-4-thiazolyl]methoxy]-1H-indole-3-acetic acid.
43. The compound of Claim 1, 1-[(phenyl)methyl]-2-methyl-5-[(2-phenyl-4-thiazolyl)methoxy]-1H-indole-3-acetic acid.
44. The compound of Claim 1, 2-methyl-5-(2-quinolinylmethoxy)-1-[[4-(2-quinolinylmethoxy)phenyl]methylene]-1H-indene-3-acetic acid.
- 25 45. The compound of Claim 1, N-[[1-[(4-chlorophenyl)methyl]-2-methyl-5-(2-quinolinylmethoxy)-1H-indol-3-yl]methyl]-N'-hydroxyurea.

- 80 -

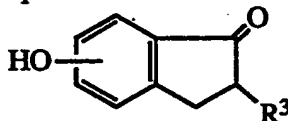
46. A process for preparing a compound of Claim 1 comprising one of the following:

a) where the final product has the formula



5 wherein R^6 is $A(CH_2)_nO-$

i) etherifying a compound of formula

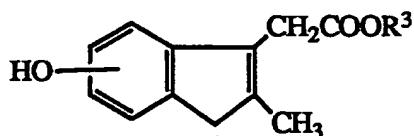


wherein R^3 is as defined above, with a compound of formula



10 where A and n are as defined above and X is a leaving group, followed by reaction with triethylphosphonoacetate, hydrolysis of the resulting acetic acid ester intermediate and then reaction with an appropriately substituted benzaldehyde to introduce the desired $R^5CH=$ moiety into the intermediate to yield the desired final product; or

ii) reacting an intermediate having the formula



15

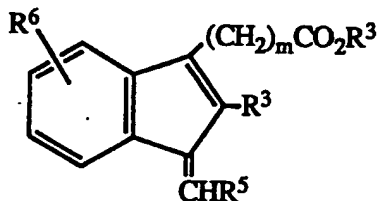
wherein R^3 in the $-COOR^3$ moiety is lower alkyl, with an appropriately substituted benzaldehyde to introduce the desired $R^5CH=$ moiety into said intermediate and then etherifying said intermediate with a compound of formula




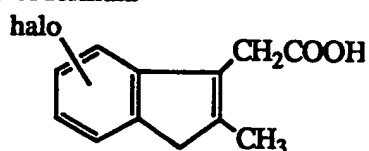
20 where A and n are as defined above, and X is a leaving group and, if necessary, hydrolyzing the intermediate to yield a final product in which R^3 is hydrogen; or

- 81 -

b) where the final product has the formula

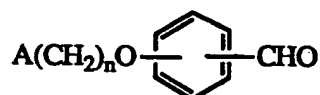


wherein R^6 is halo, R^5 represents $A(CH_2)_nO$  and R^3 and n are as defined above, reacting a compound of formula



5

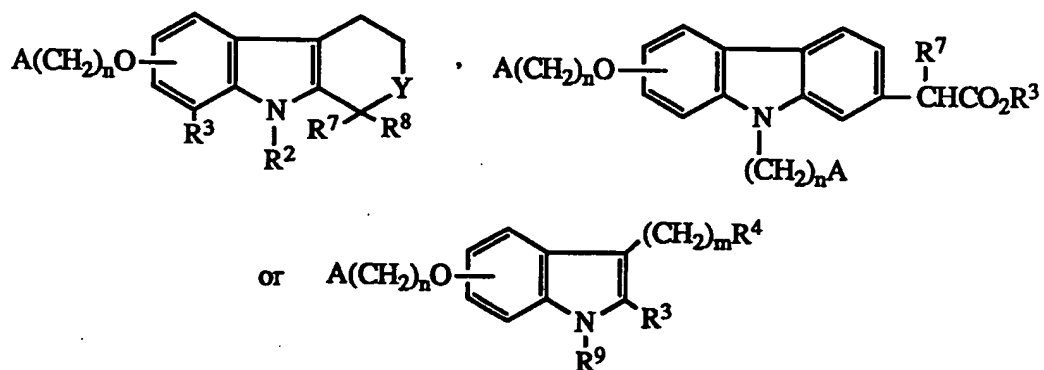
with a compound having the formula



where A and n are as defined above; and, if desired, esterifying the final product free acid;

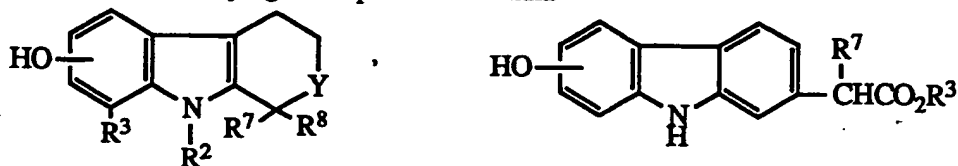
10

c) where the final products have the formula



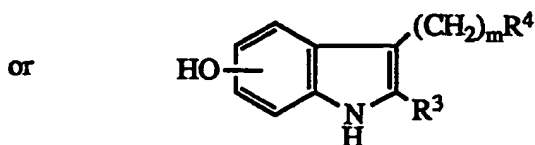
wherein Y , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , A and n are as defined above,

i) etherifying a compound of formula



15

- 82 -

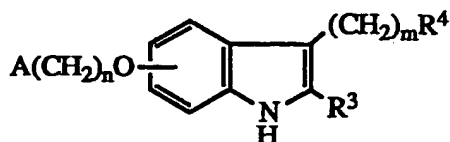


with a compound of formula

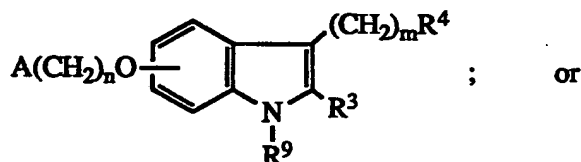


- where A and n are as defined above and X is a leaving group, and, if necessary,
 5 wherein the intermediate bears the ester function $-CO_2R^3$ or $-CO_2R^2$, hydrolyzing the intermediate, to yield a compound in which R^2 or R^3 in the moiety $-CO_2R^2$ or $-CO_2R^3$ is hydrogen; and further

- ii) reacting the intermediate compound



- 10 with a compound having the formula $R^9\text{hal}$
 wherein R^9 is as defined above and hal represents a halo atom, to yield the final product



- d) hydrolyzing a compound of formula I, II, III or IV, wherein the moiety $-CO_2R^2$ or $-CO_2R^3$ is an ester function, to yield a compound in which R^2 or R^3 in said
 15 moiety is hydrogen or a pharmacologically acceptable salt thereof; or

- e) converting a compound of formula I, II, III or IV to a pharmacologically acceptable salt.

47. A process as claimed in Claim 46 substantially or as hereinbefore described and illustrated in any one of Examples 1E, 1F, 1G, 2, 3, 4, 5B, 5C, 6C, 6E,
 20 6F, 7, 8E, 9D, 10D, 11C, 12C, 13, 14C, 15C, 16A, 16C, 16D, 17, 18, 19, 20, 21F and 22 through 42.

This Page is inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLORED OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REPERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images problems checked, please do not report the problems to the IFW Image Problem Mailbox